Organic Reactions

Organic Reactions

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In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures *illustrating* the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

CONTENTS

THE CHAPMAN REARRANGEMENT

J. W. SCHULENBERG AND S. ARCHER

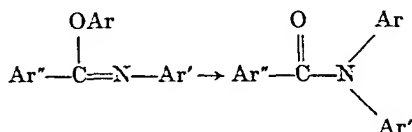*Sterling-Winthrop Research Institute, Rensselaer, New York*

CONTENTS

INTRODUCTION

The thermal conversion of aryl N-arylbenzimidates to N-aroyldiphenyl-

$$\underset{\text{Ar}''}{\overset{\overset{\displaystyle\text{OAr}}{|}}{\text{C}}}=\text{N}-\text{Ar}' \rightarrow \underset{\text{Ar}''}{\overset{\overset{\displaystyle\text{O}}{\|}}{\text{C}}}-\underset{\diagdown\text{Ar}'}{\overset{\diagup\text{Ar}}{\text{N}}}$$

amines is known as the Chapman rearrangement. The rearrangement
was discovered by Mumm, Hesse, and Volquartz who, in 1915, described
the rearrangement of the parent compound, phenyl N-phenylbenzimidate,
to N-benzoyldiphenylamine.[1] No further examples of the reaction were
reported until 1925, when Chapman's first study was published.[2] Since
he not only studied the mechanism of the reaction[3] but also first used it
as a general synthesis of diphenylamines,[4] his name is associated with this
reaction.*

The starting materials for the Chapman rearrangement have been
referred to as imino ethers, imido esters, imidates, and by a miscellany
of other names. We agree with the recommendations of Roger and
Neilson[6] and have named all compounds as imidates, i.e., as esters of the
parent imidic acid. Thus compound 1, when named as a derivative of

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[1] Mumm, Hesse, and Volquartz, *Ber.*, **48**, 379 (1915).

[2] Chapman, *J. Chem. Soc.*, **127**, 1992 (1925).

[3] Chapman, *J. Chem. Soc.*, **1927**, 1743.

[4] Chapman, *J. Chem. Soc.*, **1929**, 569.

* A broader definition which includes the rearrangement of alkyl imidates has been used.[5,6]
We prefer the more limited one for the following reasons. (1) It is in better accord with
general literature usage; Müller[7] and Gowan and Wheeler[8] employ the more restricted version.
(2) Mechanistically, the rearrangement of aryl benzimidates is distinctly different from that
of the alkyl esters. (3) Chapman himself confined his investigations, with one exception,
to aryl imidates.

benzimidic acid (2), is called *p*-chlorophenyl N-(*p*-bromophenyl)benzim-

$$OC_6H_4Cl\text{-}p \qquad\qquad OH$$
$$C_6H_5C{=}NC_6H_4Br\text{-}p \qquad C_6H_5C{=}NH$$
$$\mathbf{1} \qquad\qquad\qquad \mathbf{2}$$
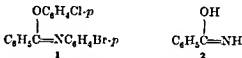
idate, in accordance with *Chemical Abstracts* usage. When named as an imino ether, the compound is called N-(*p*-bromophenyl)benzimino *p*-chlorophenyl ether.

We have not named the rearrangement products according to *Chemical Abstracts*, which lists the compounds as derivatives of benzanilide or benzamide. Since the Chapman rearrangement is used as a preparative method for diarylamines, we have stressed this fact by calling the initial products aroyldiarylamines, providing a uniform nomenclature. Similarly, we have named all the compounds obtained by amide hydrolysis as diarylamines, even though *Chemical Abstracts* often uses other names. For example, 3 is named 2'-chlorodiphenylamine-2-carboxylic acid rather
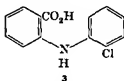
than N-(*o*-chlorophenyl)anthranilic acid. Acridones are numbered according to *Chemical Abstracts*.

MECHANISM

The Chapman rearrangement has been shown to be an intramolecular reaction in which a 1,3 shift of an aryl group from oxygen to nitrogen occurs. The reaction, which proceeds via a 4-membered transition state, may be considered as a nucleophilic attack by nitrogen on the migrating aryl group.
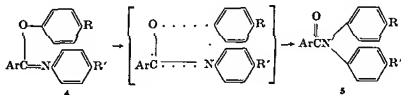
Wiberg and Rowland showed that the reaction is intramolecular by heating a mixture of phenyl N-phenylbenzimidate (4, R = R' = H) and

p-chlorophenyl N-(p-chlorophenyl)benzimidate (4, R = R′ = Cl).[9]   The infrared spectra and x-ray powder patterns of the reaction mixtures showed that the composition was the same as those obtained when the two imidates were heated separately and the products mixed.   Earlier, Chapman had performed a similar experiment with a mixture of 4 (R = R′ = H) and 4 (R = R′ = CH$_3$).   The absence of the mixed product 5 (R = H, R′ = CH$_3$) in the pyrolysis product, which was determined only from the freezing point of the mixture, led Chapman to conclude correctly that the reaction is intramolecular.[2]

Chapman[2] also used freezing point data to determine that the rearrangement of phenyl N-phenylbenzimidate followed first-order kinetics. In a later paper, however, in which a large number of imidates were pyrolyzed, he determined the percentages of the unreacted basic imidates in the mixtures by titration with acid.[3]   Since his rate data were obtained using molten imidates (no solvent), the results were probably not very accurate.   Wiberg and Rowland conducted kinetic experiments on a variety of imidates in diphenyl ether, under carefully controlled conditions, and confirmed Chapman's conclusion that the reaction is unimolecular.[9]

Chapman studied the rates of rearrangement of several imidates 6, which differed only in the substituents on the aryloxy ring.[3]   By far the most reactive was 6 (R = o-NO$_2$) since over 40% was rearranged in 90 minutes at 162–163°.   The next most reactive compound, 6 (R = 2,4,6-Cl$_3$), was unchanged at this temperature, but 87% conversion to the amide occurred when it was heated for 90 minutes at 200–201°.   The

6
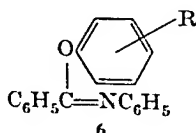
parent compound 6 (R = H) required a temperature of 266° for 90 minutes to effect 74% conversion to amide.   The least reactive compound studied, 6 (R = p-CH$_3$O) required 90 minutes at 266° for 44% rearrangement.

Chapman concluded that the rate of the reaction was associated with the acidity of the phenol from which the imidate was derived and that the rearrangement proceeded via a four-membered intermediate.   He believed that the aryl group migrated with the pair of electrons bound to oxygen. The first suggestion that the reaction is initiated by nucleophilic attack of the unshared electrons of the nitrogen atom was made in *Annual Reports*.[10]   Later Wiberg and Rowland[9] concluded from their kinetic

study that the reaction is indeed essentially a nucleophilic displacement on an aromatic ring. Electron-attracting groups on the aryloxy ring accelerate the reaction by helping to accommodate the partial negative charge induced on the ring by the nitrogen electrons. Alkyl imidates do not undergo the normal Chapman rearrangement (see p. 26) presumably because the saturated alkyl group, in contrast to an aryl group, cannot accommodate the additional negative charge.

Wiberg and Rowland studied a larger number of imidates, 6, where R is an *ortho* or a *para* substituent. In all but one case, the *ortho*-substituted compound reacted more rapidly than the *para*, confirming Chapman's earlier observations. Wiberg attributed this to an entropy effect; the *ortho* group lessened the entropy decrease in going from the reactant to the four-membered transition state. The one exception involved the *o-t*-butyl group, where steric compressibility is important. For a fuller explanation of the entropy effects, as well as a discussion of the geometric configurations of the imidates, the original paper should be consulted.[9] In a later paper Wiberg discussed the various types of reactions in which intramolecular 1,3 shifts take place.[11]

Chapman also studied several imidates which differed only in the substituents on the arylimino ring.[3] He found that compound 7 (R = *p*-CH_3O) rearranged faster than compound 7 (R = H). The imidate 7 (R = 2,4,6-Cl_3) was considerably less reactive than the parent compound. Thus electron-withdrawing groups make the electrons on nitrogen less available for nucleophilic attack and slow down the reaction. Derivatives of the imidate 8 exhibited the same behavior, but the effect
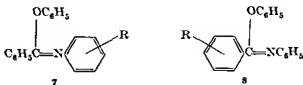
was less marked.[3] Compound 7 (R = *o*-NO_2) could not be rearranged successfully even at 220°; above this temperature decomposition occurred.[3] Owing to resonance, the electrons of arylamines are less available than those of alkylamines, and it would seem reasonable that N-alkyl imidates would rearrange readily. However, in the only case reported, the N-methyl analog of 7 decomposed without isomerizing.[3]

The imidate 6 (R = *p*-Br) rearranged more rapidly than the corresponding *p*-chloro compound, which in turn rearranged more rapidly than

[11] Wiberg and Shryne, *J. Am. Chem. Soc.*, 77, 2774 (1955).

the parent imidate **9** (R = H).[9] The parent imidate **9** (R = H) was

$$C_6H_5C=N \underset{\textstyle 9}{\overset{\textstyle O}{\bigcirc}}$$

converted to N-benzoyldiphenylamine in 80% yield by heating for 1 hour at 280°.[12] The dibromo analog **9** (R = Br) required heating for 2 hours to effect a comparable conversion. It therefore appears that in this case the effect of the substituent in the nitrogen-bonded ring is greater than that in the oxygen-bonded ring. A more dramatic effect is reported for the difluoro compound **9** (R = F), heating for 18 hours at 280° being required for 80% conversion.[12] This is attributed to the great electron-withdrawing ability of fluorine, the halide atom in the nitrogen-bonded ring again being the dominant factor. Kinetic data on a variety of compounds substituted in the nitrogen-bonded ring alone and in both rings would be of great interest for determining the relative effects of substituents in the two rings. Both monofluoro imidates **6** (R = *p*-F) and **7** (R = *p*-F) have been converted in over 80% yield to the amides upon heating at 305–310° for 1 hour.[13] However, no kinetic data are available. Rate data on the imidate **6** (R = *p*-F) would be of special interest since a *p*-fluorine atom may either accelerate or decelerate (relative to *p*-H) nucleophilic displacement.[14]

SCOPE AND LIMITATIONS

The objective of the early work on the pyrolysis of aryl imidates was to obtain information about the mechanism of the reaction, rather than to develop it for preparative purposes.[1-3] In 1929 it was pointed out that the rearrangement could serve as a general method for preparing diphenylamines by hydrolysis of the primary reaction products,[4] and a variety of substituted diarylamines has since been prepared in this way. The Chapman rearrangement has been carried out successfully with most of the imidates tried, and yields have generally been high. Unfortunately, yields have not been reported for many reactions, especially those reported in the earlier literature. The conversion of phenyl N-phenyl-benzimidate to N-benzoyldiphenylamine was said to be complete after 2 hours at 270–300° and no by-products were formed, but the yield of crystallized product was not reported.[2] Similarly it has been implied that various chloro-substituted imidates rearranged quantitatively, but yields were not given.[3]
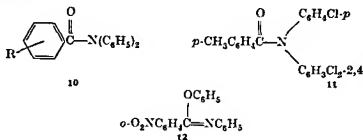
[11] Benington, Shoop, and Poirier, *J. Org. Chem.*, **18**, 1506 (1953).
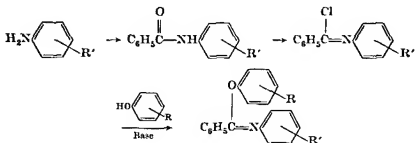[12] Schulenberg and Archer, unpublished results.
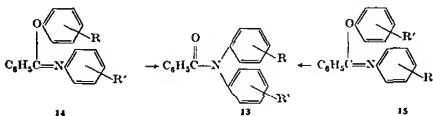[14] Sauer and Huisgen, *Angew. Chem.*, **72**, 309 (1960).

The reaction can be used also to prepare aroyldiphenylamines substituted in the aroyl ring, e.g., the compounds 10 where R is o-chloro, p-chloro, p-nitro, p-methoxy, and 2,4,6-trichloro,[9] and the even more highly substituted aroylamine 11.[15] An attempt to rearrange 12 was unsuccessful.[3]

$$R\text{—}\underset{O}{\overset{\parallel}{C}}\text{—N}(C_6H_5)_2 \qquad p\text{-}CH_3C_6H_4\underset{O}{\overset{\parallel}{C}}\text{—N}\begin{matrix}C_6H_4Cl\text{-}p\\ C_6H_3Cl_2\text{-}2,4\end{matrix}$$

<div align="center">

10   **11**

$$o\text{-}O_2NC_6H_4\overset{OC_6H_5}{\overset{\parallel}{C}}\text{=NC}_6H_5$$

12

</div>

The usefulness of the Chapman rearrangement obviously depends on the availability of the aryl imidates, which are generally prepared by the following route.

$$H_2N\text{—}\langle\langle\rangle\rangle\text{—}R' \rightarrow C_6H_5\text{—}\underset{O}{\overset{\parallel}{C}}\text{—NH}\text{—}\langle\langle\rangle\rangle\text{—}R' \rightarrow C_6H_5\text{—}\overset{Cl}{\overset{\parallel}{C}}\text{=N}\text{—}\langle\langle\rangle\rangle\text{—}R'$$

$$\xrightarrow[\text{Base}]{HO\text{—}\langle\langle\rangle\rangle R} \quad C_6H_5\overset{R}{\overset{\langle\langle\rangle\rangle}{\overset{O}{C}}}\text{=N}\text{—}\langle\langle\rangle\rangle R'$$

For the preparation of unsymmetrically substituted diarylamines **13**, either of two imidates, **14** or **15**, may be utilized. The choice between

$$C_6H_5C\overset{R}{\underset{\langle\langle\rangle\rangle}{\overset{O}{\parallel}}}\text{=N}\langle\langle\rangle\rangle R' \rightarrow C_6H_5\underset{O}{\overset{\parallel}{C}}\text{—N}\begin{matrix}R\\ R'\end{matrix} \leftarrow C_6H_5C\overset{R'}{\underset{\langle\langle\rangle\rangle}{\overset{O}{\parallel}}}\text{=N}\langle\langle\rangle\rangle R$$

<div align="center">

14   **13**   **15**

</div>

14 and 15 is often dictated by the relative availabilities of the amine and the phenolic components. When both sets of reagents are available, the imidate selected is usually the one which will rearrange at the lower temperature. Therefore the more acidic phenol (with electron-withdrawing substituents) should be chosen.[4] In several cases, both imidates have

[15] Jamison and Turner, *J. Chem. Soc.*, 1937, 1954.

been used successfully. For example, all six possible monochloroimidates have been prepared and pyrolyzed to the three isomeric N-benzoylchlorodiphenylamines.[2,3] On the other hand, while the imidate **14** (R = o-NO$_2$, R' = H), was converted in 40% yield to N-benzoyl-o-nitrodiphenylamine in 1 hour at 165°, the isomeric compound **14** (R = H, R' = o-NO$_2$) did not rearrange.[3]

A great variety of halogenated diarylamines has been prepared by the Chapman rearrangement: the monochlorodiphenylamines previously mentioned and a large number of dichloro-, trichloro- and tetrachlorodiphenylamines.[3,4,15-20] The pentachloro imidate **14** (R = 2,4,6-Cl$_3$, R' = 2,4-Cl$_2$) was converted to the N-benzoyldiarylamine in 81% yield, and this product was then hydrolyzed to 2,2',4,4',6-pentachlorodiphenylamine in 92% yield.[15] The hexachloro compound **14** (R = R' = 2,4,6-Cl$_3$) has also been rearranged successfully.[3]

N-Benzoyl-2,2'-dibromodiphenylamine[21] and its 4,4'-dibromo analog[22] have been prepared and hydrolyzed to the diphenylamines. In the former case the rearranged product was obtained in 86% yield, and its hydrolysis product in 87% yield. The iodine-containing imidates **16a** and **16b** were rearranged to the N-benzoyldiphenylamines in 56% and 95% yields, respectively.[23]

$$C_6H_5C{=\!\!=}NC_6H_4OCH_3\text{-}p$$

16

(a, R = CH$_3$; b, R = CO$_2$CH$_3$)
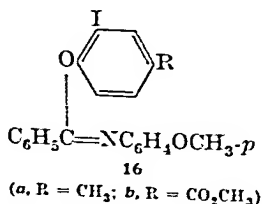
Pyrolysis of the fluorine-containing imidate, **14** (R = R' = p-F), has been reported to furnish N-benzoyl-4.4'-difluorodiphenylamine (80% yield) which was hydrolyzed almost quantitatively to 4,4'-difluorodiphenylamine.[12]

The first alkyl-substituted aryl imidate to be pyrolyzed was the dimethyl derivative **14** (R = R' = p-CH$_3$) which was converted to N-benzoyl-4.4'-dimethyldiphenylamine.[2] A little later the synthesis of several monomethyl- and dimethyl-diphenylamines via the Chapman route was

reported [24,25] Two of these, 3-methyldiphenylamine [24] and 2,3'-dimethyldiphenylamine,[25] were each prepared via both isomeric imidates. 4-Methyldiphenylamine was synthesized in an overall yield of 84% based on the imidate 14 (R = H, R' = p-CH₃).[26]

Wiberg and Rowland prepared and rearranged two ethyl-substituted imidates, 14 (R = o-C₂H₅, R' = H) and 14 (R = p-C₂H₅, R' = H), and the corresponding isopropyl compounds but did not isolate any of the four alkylbenzoyldiphenylamines.[9] The same workers pyrolyzed a large number of imidates for their kinetic study, but the only product isolated was the t-butyl compound 17 (40% yield).[9] N-Benzoyl-4,4'-di-t-butyldiphenylamine was reported much earlier as resulting in "almost quantitative" yield by heating the corresponding imidate at 300°.[27] Benzyl groups are stable at the temperature required for the Chapman rearrangement. Both benzylphenyl imidates 18 were converted to the desired aroyldiphenylamines in over 80% yield by heating at 275°.[28]

17

18

(a = o-C₄H₉C₆H₄, b = p-C₄H₉C₆H₄)
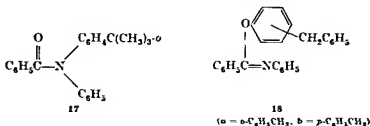
In addition to alkyl- and halogen-substituted imidates, compounds bearing methoxy, nitro, acetyl, benzoyl, cyano, and carbalkoxy groups have been rearranged. The three isomers of 14 (R' = H, R = OCH₃), as well as 14 (R = H, R' = p-OCH₃), were converted to N-benzoyldiphenylamines.[3] Since then, the iodo-methoxy imidates[25] 16 and the dicyano-methoxy imidate[29] 19 have been rearranged.

19

14
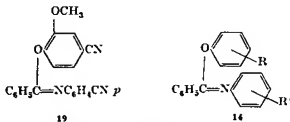
[24] Gibson and Johnson, *J. Chem. Soc.* 1929, 1473.

[25] Gibson and Johnson, *J. Chem. Soc.* 1929, 2743.

[26] Hey and Moynehan, *J. Chem. Soc.* 1959, 1563.

[27] Craig, *J. Am. Chem. Soc.*, 57, 195 (1935).

[28] Waters and Watson, *J. Chem. Soc.* 1957, 253.

[29] Easson, *J. Chem. Soc.*, 1961, 1029.

Compounds 14 (R = o-NO$_2$. R′ = H[3] and R = o-NO$_2$, R′ = 2-Br, 4-CH$_3$[30]) were converted to the desired benzoyldiarylamines by heating for 1 hour at less than 200°, but under similar treatment 14 (R = p-NO$_2$, R′ = H and R = H, R′ = o-NO$_2$) decomposed to tarry materials.[3] No m-nitro compounds have been studied.

Only three acyl-substituted imidates have been subjected to pyrolysis. The $para$-substituted compounds 14 (R = p-CH$_3$CO, R′ = H[3] and R = p-C$_6$H$_5$CO. R′ = H[31]) reacted normally. The latter gave N,4-dibenzoyldiphenylamine (90% yield), which on hydrolysis lost the N-benzoyl group and furnished the diarylamine in 89% yield. The o-acetyl compound 20 when pyrolyzed at 267° gave the quinoline derivative 22.[2] The normal Chapman rearrangement product, 21, was an intermediate in this reaction.
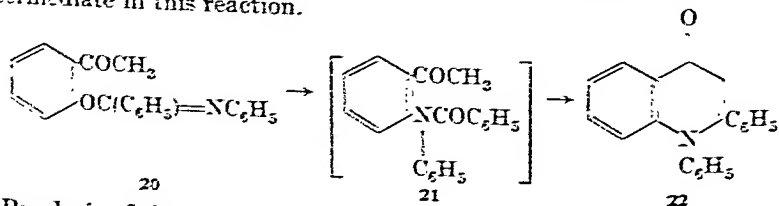

Pyrolysis of the appropriate imidate at 280–300° furnished N-benzoyl-4,4′-dicyanodiphenylamine (23).[32] Hydrolysis with sodium hydroxide in ethylene glycol afforded 4,4′-dicyanodiphenylamine (25). Ammonolysis of the nitrile 23 gave the diamidino compound 24 which, when heated, gave benzamide and the diarylamine 25 in 76% yield.
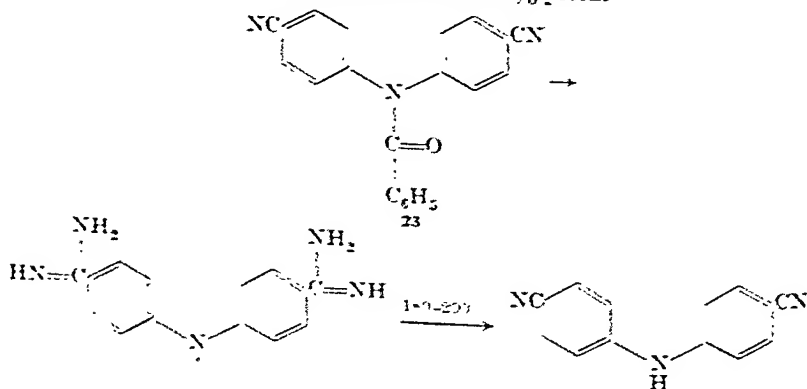
Several derivatives of the dinitrile 23 substituted in the *ortho* positions have been prepared by the Chapman rearrangement in high yield.[29] For example, the imidate 14 (R = 2-Cl, 4-CN, R' = *p*-CN) heated in boiling Dowtherm furnished the o-chloro analog of 23 in 84% yield. Hydrolysis in ethylene glycol gave 2-chloro-4,4'-dicyanodiphenylamine in 60% yield. The 2-methoxy compounds, analogs of 23 and 25, were similarly prepared in yields of 88% and 86%, respectively. The imidate 14 (R = 2-NO₂, 4-CN, R' = *p*-CN) was quantitatively rearranged in either boiling anisole or pyridine, but the product could not be hydrolyzed cleanly to 4,4'-dicyano-2-nitrodiphenylamine. The last-named compound was synthesized by nitration of the dicyanodiphenylamine 25.[29] Only two cyano-containing imidates, 14 (R = *p*-CN, R' = 2-NO₂, 4-CN and R = R' = 2-NO₂, 4-CN), that could not be rearranged to the appropriate diphenylamine have been reported.[29]

The conversion of 14 (R = *p*-CO₂CH₃, R' = H) to N-benzoyl-4-carbomethoxyphenylamine in high yield has been reported by two groups of investigators.[26,33] Hydrolysis to diphenylamine-4-carboxylic acid proceeded smoothly in 73% yield.[26] Attempts to isomerize the *meta*-substituted ester analog (14, R = *m*-CO₂CH₃, R' = H),[33] the corresponding carboxylic acid,[33] or the ester 26 failed.[34] The rearrangement of derivatives of salicylic acid is discussed on pp. 13–15.
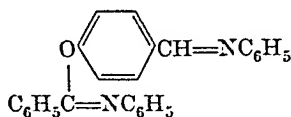

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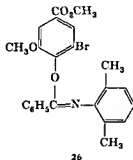
The imidates 27 containing aldehyde groups could not be rearranged.[23,33] However, the anil 28 pyrolyzed at 270° to furnish presumably the expected
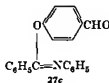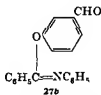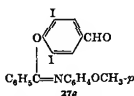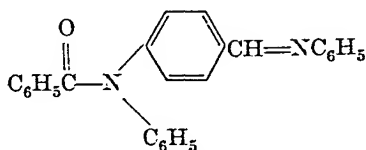
33 Brown, Carter, and Tomlinson, *J. Chem. Soc.*, 1958, 1843.
34 Harris, Potter, and Turner, *J. Chem. Soc.*, 1955, 145.

rearrangement product **29**, which, however, could not be hydrolyzed to N-benzoyldiphenylamine-4-carboxaldehyde.[33]

28

29

Only one abnormal Chapman rearrangement has been reported, excluding those examples where the normal product results and then reacts further.[35] The carbomethoxymethyl derivative **30** on pyrolysis gave a mixture from which two products, each obtained in 29% yield, were identified. One was shown to be the normal rearrangement product **31**; hydrolysis with base followed by acidification gave the expected N-phenyloxindole (**32**).
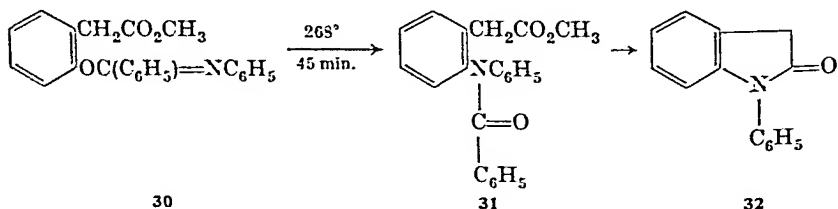
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31

32

The other product was 3-benzanilimino-2(3H)benzofuranone (**34**). The following mechanism involving basic catalysis (imidates are weakly basic) and rearrangement of the anion **33** was proposed.[35] The imidate **30** on

33

treatment with sodium methoxide in boiling benzene furnished the furanone 34 in 56% yield, showing the feasibility of the proposed base-catalyzed reaction.[35] Other imidates with active hydrogen atoms on the 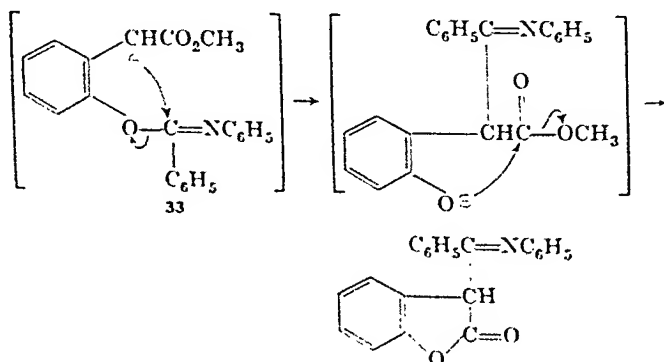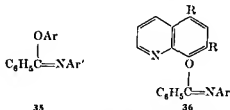*ortho* substituent could also be expected to give abnormal pyrolysis products. In these cases the isomeric imidates should be used to prepare the desired aroyldiphenylamines.

Relatively few imidates containing aryl groups other than phenyl or substituted phenyl groups have been rearranged. Chapman pyrolyzed the three naphthyl derivatives 35. The first two gave N-benzoyl-N-phenyl-α-naphthylamine; the third gave the corresponding β-naphthyl-amine.[3]

$$C_6H_5C\begin{array}{c}OAr\\\\ \backslash NAr'\end{array}$$

35

(*a*, Ar = C$_6$H$_5$, Ar' = α-C$_{10}$H$_7$) (*b*, R = H, Ar = C$_6$H$_5$)
(*b*, Ar = α-C$_{10}$H$_7$, Ar' = C$_6$H$_5$) (*c*, R = H, Ar = o-CH$_2$C$_6$H$_4$)
(*c*, Ar = β-C$_{10}$H$_7$, Ar' = C$_6$H$_5$) (*c*, R = Cl, Ar = C$_6$H$_5$)
(*d*, R = H, Ar = o-ClC$_6$H$_4$)
(*e*, R = H, Ar = 2-Br-4-CH$_3$C$_6$H$_3$)
(*f*, R = H, Ar = 2-Br-4,6-(CH$_3$)$_2$C$_6$H$_2$)

Hall pyrolyzed the six 8-quinolinyl imidates 36; the first in 72% yield, the second and third in unspecified yield, and the remaining three unsuccessfully.[30]

Hey and Moynehan rearranged three imidates 37 derived from phenanthridine;[26] the phenoxy derivative (R = H) to the phenanthridone 38 in 60% yield, the analogs (R = Cl) and (R = CH$_3$) in 75% and 70% yields, respectively.

37   38
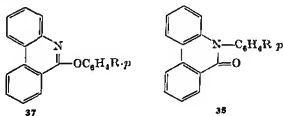
Diphenylamine-2-carboxylic Acids

The Chapman rearrangement of imidates in which the phenolic component is a salicylic acid derivative serves as a synthesis of derivatives

of diphenylamine-2-carboxylic acid (N-phenylanthranilic acid). The development of this synthesis is due to Jamison and Turner who showed that the parent imidate **39** (R = R′ = H), prepared from methyl salicylate and N-phenylbenzimidoyl chloride, rearranged readily to the aroylamine **40** in 73% yield on heating for 10 minutes at 270–275°. Hydrolysis of the aroylamine with 1 mole of base gave the N-benzoyl acid **41** in 76% yield, and excess base gave diphenylamine-2-carboxylic acid (**42**) in 96% yield.[15] (In a later paper the yield was reported as 78%.[36])
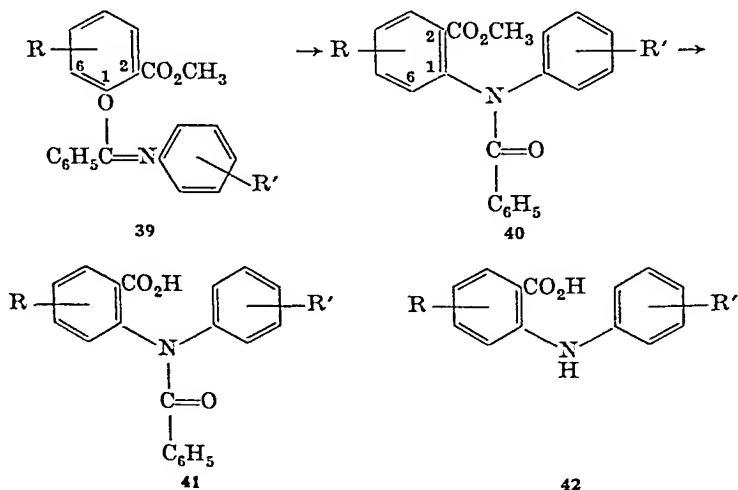
The rearrangement of a variety of substituted imidates also proceeded well, usually in better than 80% yield. Among these were chloro, bromo, methoxy, and methyl analogs of **39**.[15] Later a large number of imidates derived from 3-methylsalicylic acid were rearranged, for example, the imidates **39** in which R = 6-CH$_3$ and R′ = H, o-F, o-Cl, o-Br, and o-CH$_3$.[34,36,37] The rearrangement products were all partially hydrolyzed to the corresponding N-benzoyl acids **41**,[15,34,36–39] many of which were partially or completely resolved and their optical stabilities studied.[34,37–39] The only imidate that could not be isomerized to the desired aroyldiphenylamine was **39** in which R = 6-CH$_3$ and R′ = 2,4,6-(CH$_3$)$_3$.[34]

The imidate 30 derived from *o*-hydroxyphenylacetic acid gave a mixture of a benzofuranone and the normal rearrangement product on pyrolysis. (See p. 12.) However, the compounds 39 (R = H, R' = *o*-CH₂CO₂CH₃ or *o*-CH₂CO₂C₂H₅), containing a carbalkoxymethyl substituent in the phenyl group bonded to nitrogen, rearranged normally in 83% and 91% yield, respectively.[41]

Acridones

Jamison and Turner were also the first to use the products of the Chapman rearrangement as intermediates for the synthesis of acridones[15] 2-Chloroacridone (46) was prepared by them in three different ways. The aroylamine 43, (which had been prepared by heating the appropriate imidate at 270°) was pyrolyzed at 320°, yielding methyl benzoate and the acridone 46. The yield was "not quantitative" The second route involved partial hydrolysis to the acid 44 which was heated for 5 minutes at 250°. Benzoic acid was eliminated and the acridone 46 obtained in 90% yield. The third path utilized the completely hydrolyzed acid 45 which was converted to 46 by treatment with phosphorus oxychloride and hydrolysis of the resulting 2,9-dichloroacridine,[45] the over-all yield was 87%.[15]
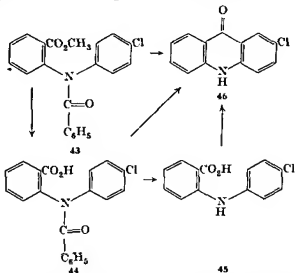
[40] G. Singh, S. Singh, A. Singh, and M Singh, *J. Indian Chem Soc*, 29, 783 (1952).

[41] G. Singh, S. Singh, S. Singh, and M' Singh, *J. Indian Chem. Soc*, 28, 698 (1951)

[42] G. Singh, S. Singh, A. Singh, and M. Singh, *J. Indian Chem Soc*, 28, 459 (1951).

[43] S. Singh, *J. Sci. Ind. Res. (India)*, 10B, 82–6 (1951) [*C A*, 46, 2547 (1952)].

[44] Schulenberg and Archer, *J. Am Chem Soc*, 83, 3091 (1961)

[45] N. S. Drozdov and S. S. Drozdov, *J. Gen. Chem. USSR (Engl. Transl)*, 4, 1 (1934) [*C.A.*, 28, 5456 (1934)]; N. S. Drozdov, *ibid.*, 4, 117 (1934) [*C.A*, 28, 5456 (1934)].

Surprisingly, the parent compound **47** (R = R′ = H) did not give acridone at temperatures as high as 350°.[15]   On the other hand, the acid **47** (R = H, R′ = 2,4(CH₃)₂) formed 2,4-dimethylacridone in 71% yield when it was pyrolyzed at 300° for a few minutes, but the corresponding ester did not give the acridone when heated at 350°.[15]

Pyrolysis of compounds **47** (R = 4-Cl, R′ = *p*-OCH₃) and **47** (R = 6-CH₃, R′ = *o*-Cl) gave, respectively, the acridones **48**, in almost quantitative yield,[15] and **49** in 86% yield.[36]   The phosphorus oxychloride method was used for the preparation of the acridone **50** in 91% yield.[15]
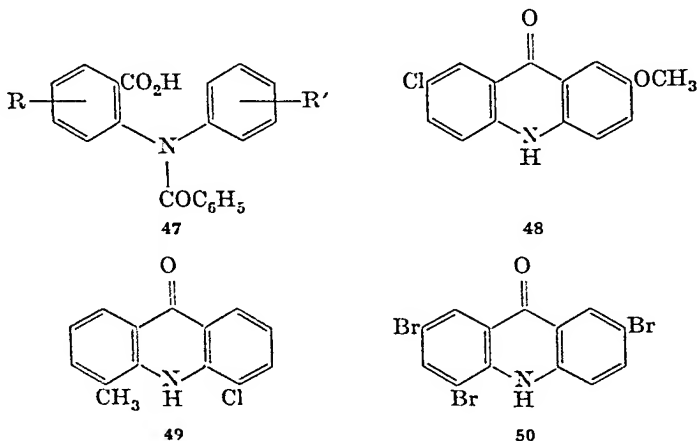
2-Chloro-6-methoxyacridone was prepared in unspecified yields by all three routes.[42]   The isomeric 5-chloro-3-methoxyacridone was prepared by the two pyrolytic methods,[40] while an acridone, believed to be the 1-chloro-6-methoxy isomer, was synthesized by the phosphorus oxychloride route.[41]   2-Iodo-6-methoxyacridone was also synthesized by pyrolysis of the ester and by the phosphorus oxychloride method.[43]   In all cases the starting imidate was that derived from 4-methoxysalicyclic acid.[40–43]

1,9-Dichloro-7-methoxyacridine (**51**) was prepared as shown in the
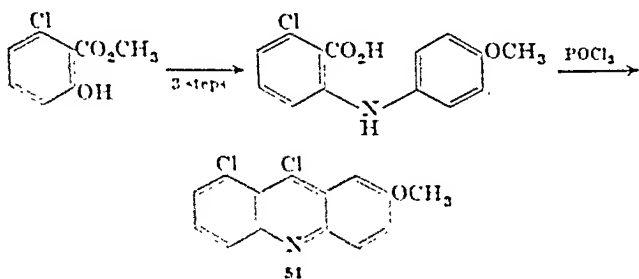
accompanying formulation.[46] The over-all yield was 28% based on methyl 6-chlorosalicylate. Ionescu synthesized 2,4,5,7-tetrachloroacridone (53) in 10% yield by heating the imidate 52 for 10 minutes at 260° and, *without* isolating the product, heating for 1 minute at 200° with concentrated sulfuric acid.[47]

52   53
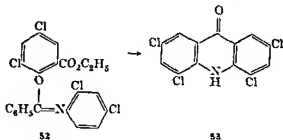
The synthesis of acridones with additional fused rings, using the Chapman rearrangement, was first accomplished by Cymerman-Craig and Loder.[48] They pyrolyzed the imidate 54 which rearranged and lost methyl benzoate to form the benzacridone 55 in 72% yield. The intermediate benzoyldiarylamine was not obtained.

54

55
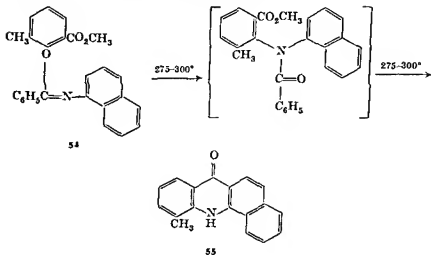
Similarly the β-naphthyl analog of 54 gave the acridone 56 in 38% yield on pyrolysis for 30 minutes at 360°, and the imidate 57 gave the pentacyclic acridone 58 in 47% yield on pyrolysis.[48]

46 Dauben and Hodgson, *J. Am Chem. Soc.*, 72, 3479 (1950)

47 Ionescu, Goia, and Felmeri, *Acad Rep. Populare Romine, Filiala Cluj, Studii Cercetari Chem*, 8, 351 (1957) [*C.A.*, 54, 4587 (1960)]. Ionescu and Goia, *Rev Chim Acad Rep. Populare Roumaine*, 5, No. 1, 85 (1960) [*C.A.*, 55, 9402 (1961)]

48 Cymerman-Craig and Loder, *J. Chem. Soc*, 1955, 4309

56

57   58
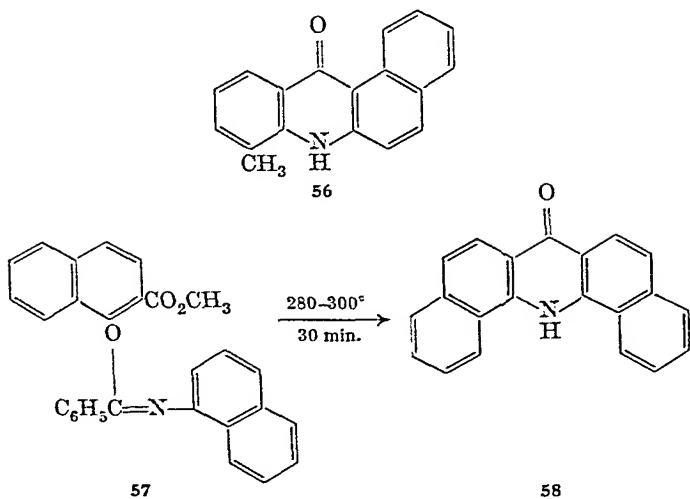
Two other pentacyclic acridones, 59 [48] and 60, [49] were synthesized in 54% and 80% yield, respectively, as indicated in the equations, but an attempt to prepare the hexacyclic acridone 61 failed.[48]

59

60

61
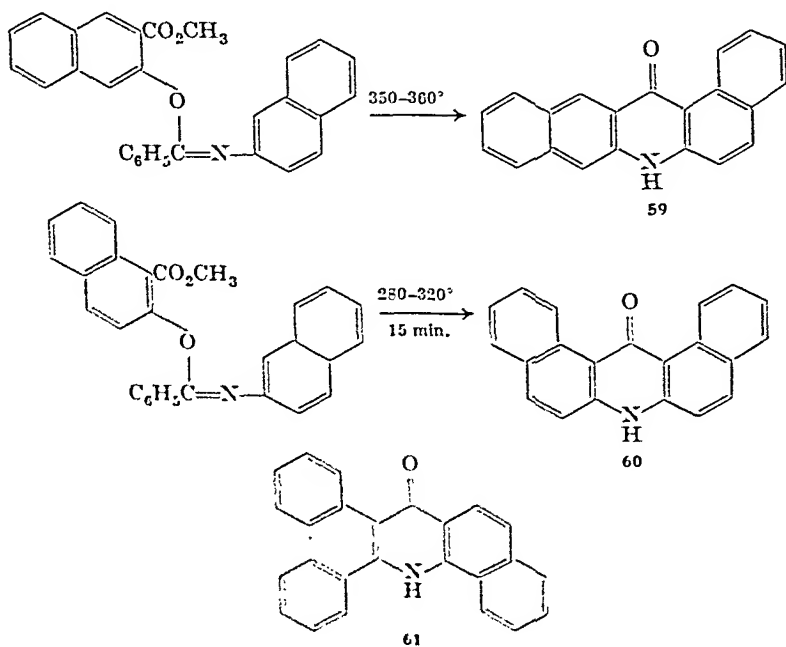
COMPARISON WITH OTHER METHODS

The majority of substituted diphenylamines reported in the literature has been prepared by direct nucleophilic displacement of halide by aromatic amines. The uncatalyzed reaction, discovered by Jourdan,
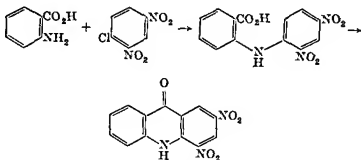
proceeds only with highly activated halides such as 2,4-dinitrochlorobenzene.[89,50] The copper-catalyzed reaction, known as the Ullmann condensation,[89,51,52]
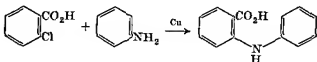
is of much greater general utility.[50,53,54] This reaction has been applied chiefly to the synthesis of diphenylamines substituted with nitro or carboxyl groups. If diphenylamines that do not contain nitro or carboxyl groups are desired, a two-step procedure may be used: an Ullmann reaction between aniline or a substituted aniline and an o-chlorobenzoic acid, followed by thermal decarboxylation of the product. The Goldberg diphenylamine synthesis,
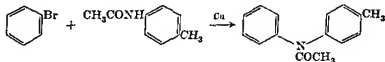
[50] Albert, *The Acridines*, E. Arnold and Co., London, 1951, p. 42.
[51] Surrey, *Name Reactions in Organic Chemistry*, Academic Press, New York, 1961, p. 236.
[52] Ullmann, *Ber.*, **36**, 2382 (1903).
[53] Bunnett and Zahler, *Chem. Rev.*, **49**, 392 (1951).
[54] Acheson, *Acridines*, Interscience Division, John Wiley and Sons, New York, 1956, p. 148; (a) p. 157; (b) p. 105.

the reaction of N-acylanilines with aryl halides followed by hydrolysis, is a copper-catalyzed reaction also.[8c,55-57]

The Chapman synthesis involves five steps from the starting aniline: benzanilide formation, conversion to imidoyl chloride, imidate synthesis, rearrangement, and hydrolysis. All five steps are easily carried out and two of the intermediates, the imidoyl chloride and the rearrangement product, are often not isolated. However, the Ullmann synthesis will generally require less time and, if other factors are equal, is to be preferred.

It is difficult to compare the yields by these two routes since, for most of the examples of the Chapman method, yields are not given in all steps. This is especially true in the early literature where the preparation of most of the simpler diphenylamines is reported. Furthermore, many of the N-benzoyldiphenylamines were not hydrolyzed. Although a huge number of derivatives of diphenylamine-2-carboxylic acid has been prepared by the Ullmann condensation, only a small percentage has been decarboxylated; most have been converted to acridine derivatives.[50,54] Some of the yields reported in the early literature are questionable. Ullmann reported that o-toluidine and o-chlorobenzoic acid could be converted to 2-methyl-diphenylamine in an over-all yield of 87% (the decarboxylation was claimed to be quantitative).[53] In a recent paper an over-all yield of 33% was reported.[59] The corresponding o-chloro and o-methoxy compounds were obtained in 69% and 52% over-all yields, respectively.[59] The corresponding yields via the Chapman synthesis are not available.

Yields are reported for imidate formation,[9,24] rearrangement,[24] and hydrolysis[24] in the preparation of 3-methyldiphenylamine. When the higher yield reported for the imidate synthesis is used,[9] an over-all yield of 35% can be estimated. Ullmann reported a 62% yield in the reaction between o-chlorobenzoic acid and m-toluidine, but no yield was given for the decarboxylation.[53] Ullmann claimed that the corresponding 4-methyl acid, obtained in 89% yield from p-toluidine, was decarboxylated quantitatively.[53] 4-Methyldiphenylamine was synthesized from phenol and benz-p-toluidide by the Chapman route in 74% over-all yield.[26]

A large number of chloro-substituted diphenylamines was prepared by Elson and Gibson by Ullmann condensation of o-chlorobenzoic acid and various aniline derivatives.[19] The products from 2,5-dichloroaniline and 3,4-dichloroaniline were decarboxylated in 85% and 75% yields, respectively, but no yields were reported for the condensation reaction.[19]

Over-all yields (three steps) for several dihalodiphenylamines prepared by the Chapman route are very similar. 4,4'-Difluorodiphenylamine was synthesized in 48% yield,[12] the corresponding 4,4'-dibromo compound was obtained in 43% yield,[22] and the dichloro analog was prepared in 47% yield.[15] Good over-all yields were obtained for the following more highly substituted compounds: 2,4,4'-trichlorodiphenylamine, 62%;[15] 2-methyl-4,4'-dicyanodiphenylamine, 61%;[29] and 2,2',4,4',6-pentachlorodiphenylamine, 66%.[15] Although direct comparison of the two methods is not possible, it seems evident that at least comparable yields are attainable by the longer route.

Frequently the choice between the two methods will depend on availability of starting materials. Often the needed o-chlorobenzoic acid will be difficult to obtain, whereas the corresponding phenol will be available. In this case the Chapman route will obviously be preferred. It must be kept in mind that there are always *at least* two sets of reagents leading to a diphenylamine via the Ullmann condensation and decarboxylation. To illustrate, the diarylamine 62 can be prepared in the following ways
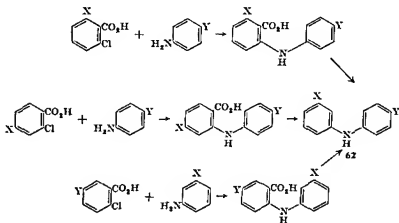
If Y were a *meta* or *ortho* substituent, a fourth possibility would exist. Furthermore, anthranilic acids will react with derivatives of bromobenzene to give diphenylamine-2-carboxylic acids.[60] Although chloro compounds are generally unreactive and bromo compounds must be used, the method has the advantage that some substituted anthranilic acids are commercially available while the corresponding o-chloro acids are not.[60] Therefore the following three sets of reagents must also be considered for the synthesis of 62.

[60] Goldberg, *Ber.*, **39**, 1691 (1906).
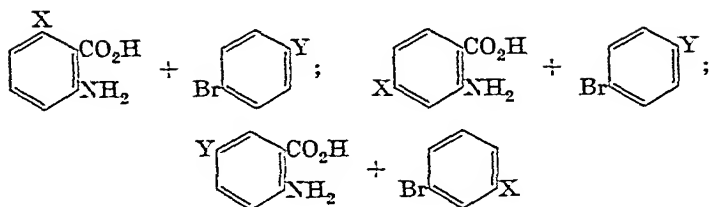
For the Chapman synthesis only two sets of compounds must be considered.
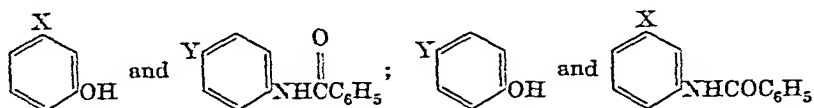
The Goldberg synthesis appears to be the preferred method for some of the simpler compounds. When p-chloroacetanilide and bromobenzene were treated with copper, potassium iodide, and iodine and the resulting product was hydrolyzed, 4-chlorodiphenylamine resulted in 72% yield.[61] Earlier, Goldberg[55] reported the conversion of m-nitroacetanilide and bromobenzene to 3-nitrodiphenylamine in 80% yield. Weston and Adkins studied thoroughly the reaction between acet-p-toluidide and bromobenzene, determining the effects of changes in catalyst and solvent.[57] Davis and Ashdown synthesized a large number of nitrodiphenylamines by the Goldberg procedure but gave no yields.[56] They also reported, without yields, the synthesis of nitrodiphenylamines from the unacetylated nitroanilines.[56] Earlier Goldberg had reported the direct conversion of o-nitroaniline and bromobenzene to 2-nitrodiphenylamine in 75–80% yield.[55]

The Ullmann condensation suffers some drawbacks, a major one being that reductive dehalogenation may sometimes become the major reaction.[53] Limitations of the reaction are discussed by Acheson.[54?]

When the appropriate o-chlorobenzoic acid is readily available, the Ullmann route will generally be preferred for the preparation of diphenylamine-2-carboxylic acids and the acridones derived from them. The parent acid itself has been prepared in 82–93% yield by the Ullmann procedure (one step),[62] while the three-step Chapman method from methyl salicylate and N-phenylbenzimidoyl chloride gave an over-all yield of 57%.[15] In a later paper lower yields were reported for the same Chapman route.[26] However, 4'-chlorodiphenylamine-2-carboxylic acid was prepared in about 75% over-all yield using the Chapman rearrangement, so the two methods may give comparable yields in some cases.[15] If the

necessary o-chloro acid is not available, the Chapman rearrangement may well be preferable since it proceeds particularly well with derivatives of methyl salicylate.[15,34,36,37]

Some Chapman rearrangement products can be converted directly to acridones by heating, but this does not appear to be a general reaction.[15] When the thermal reaction is possible, acridones may be synthesized in two steps from derivatives of methyl salicylate, so this route may in some cases be the preferred one, particularly in the synthesis of acridones with additional fused rings.[43] For example, 1,2,7,8-dibenzoacridone (60) (p. 18) was prepared by this method in 80% yield from the imidate after the Ullmann condensation between β-naphthylamine and 2-chloro-1-naphthoic acid was found to give only 1–2% of the desired diarylamine.[49]

In addition to the Ullmann and Chapman routes, a few other methods for synthesizing diphenylamines may be mentioned. Some compounds may be prepared by substitution of diphenylamine, e.g., 4,4′-dibromodiphenylamine by direct bromination[63] This compound has also been prepared via the Chapman rearrangement.[22] Certain symmetrical compounds may be prepared by the reaction of equimolar amounts of an amine and its hydrochloride. Diphenylamine itself is best prepared in this way from aniline and aniline hydrochloride.[7a] Occasionally, unsymmetrical amines are also prepared by this method, but the mixed product must be separated from the three-component mixture that is obtained.[7a]

Diphenylamines may also be prepared by the reaction between an amine and a phenol.[7b] The parent compound has been synthesized by heating aniline and phenol at 250° with antimony trichloride as the catalyst.[53] The reaction between nitrobenzene and phenylmagnesium bromide is reported to give diphenylamine in 58% yield[65] Similarly, methyl p-nitrobenzoate and phenylmagnesium bromide gave 4-carbomethoxydiphenylamine in 45% yield.[66] In contrast, the Ullmann condensation between iodobenzene and methyl p-aminobenzoate gave the same product in only 27% yield.[67] The corresponding acid has also been synthesized in 46% yield via the Chapman route starting with methyl p-hydroxybenzoate and N-phenylbenzimidoyl chloride.[26]

Finally, one example should be cited in which the Chapman method gave a good yield of the desired amine after several other routes failed completely. Jones and Mann[21] were unable to synthesize 2,2′-dibromodiphenylamine from o-chloronitrobenzene and o-bromoaniline, from

[63] Galatis and Megaloikonomos, *Prakt. Akad. Athenon*, 9, 20 (1934) [*Chem. Zentr.*, 105, II, 2974 (1934)]

[7a] Buch, *Ber.*, 17, 2634 (1884).

[65] Gilman and McCracken, *J. Am. Chem. Soc.*, 51, 821 (1929).

[66] Curtin and Kauer, *J. Am. Chem. Soc.*, 75, 6041 (1953).

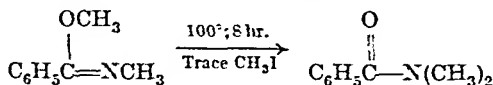[67] Gilman and Brown, *J. Am. Chem. Soc.*, 62, 3208 (1940).

o-bromoaniline and its hydrochloride, from o-bromophenol and o-bromo-aniline (with a zinc chloride catalyst), or from o-chloronitrobenzene and the sodium salt of o-bromoacetanilide. The Chapman route gave the desired product in 36% over-all yield.[21]

RELATED REACTIONS

There are several imidate-amide rearrangements which present many features of interest but which do not have the usefulness of the Chapman rearrangement. In this section these related reactions are discussed, but completeness of coverage is not attempted.

Catalyzed Rearrangements of Alkyl Imidates

The conversion of alkyl imidates to amides has been reported by many investigators, but the first careful study was that of Lander who found that the r action proceeds well when catalyzed by small amounts of an alkyl halide. The rearrangement shown in the accompanying equation is typical of many others described by Lander.[68]

$$\underset{C_6H_5C=NCH_3}{\overset{OCH_3}{|}} \xrightarrow[\text{Trace } CH_3I]{100^\circ;\,8\,\text{hr.}} \underset{C_6H_5C-N(CH_3)_2}{\overset{O}{\|}}$$

Dialkyl sulfates have been used as catalysts for the conversion of O-alkyl lactims to N-alkyl lactams.

(Ref. 69)

63

(Ref. 70)
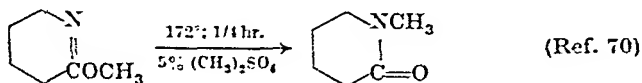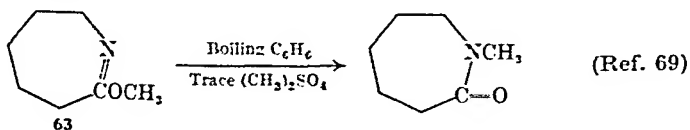
When O-ethyl caprolactim (the ethyl homolog of 63) was heated with di-methyl sulfate, a mixture of the N-methyl and N-ethyl lactams resulted.[70] Acylic analogs gave similar results.[68] In contrast to the Chapman reaction, the Lander rearrangement is intermolecular. Arbuzov has recently made use of the intermolecular nature of the reaction by treating alkyl imidates with various halides.[71] The following reaction has been carried out in 90% yield.[71]

$$C_6H_5C \overset{\underset{\displaystyle OC_2H_5}{|}}{=} NC_6H_5 + C_6H_5CH_2I \rightarrow C_6H_5C \overset{\underset{\displaystyle \parallel}{O}}{-} N(C_6H_5)CH_2C_6H_5$$
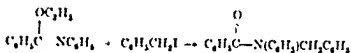
Roberts and Vogt studied the rearrangement of alkyl imidates in the presence of sulfuric acid. The accompanying reaction was carried out in 41-53% yield.[72] The reaction proceeded in better yield (74-85%)

$$HC \overset{\underset{\displaystyle OC_2H_5}{|}}{=} NC_6H_5 \xrightarrow[H_2SO_4]{170-180° \ 12 \ hr.} \overset{\underset{\displaystyle \parallel}{O}}{HC} - N \overset{\nwarrow C_2H_5}{\underset{\searrow C_6H_5}{}}$$

$$\underset{64}{} \qquad\qquad\qquad \underset{65}{}$$
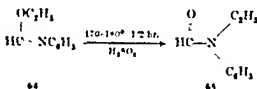
when a half mole of triethyl orthoformate was present in the reaction mixture. The p-chloro analog of 64 was rearranged in 63% yield without the use of additional orthoformate while the O-methyl analog gave N-methylformanilide in 61% yield.[72] Treatment of 64 with sulfuric acid and triisoamyl orthoformate furnished a mixture of the N-ethyl (65) and N-isoamyl amides.[72] Thus it is clear that the reaction is intermolecular and analogous to the Lander rearrangement. Presumably, the sulfuric acid generates an alkylating species from the ortho ester (and from the imidate) which is equivalent to the alkyl halide catalyst used by Lander.
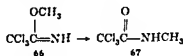
Since ethyl N-phenylformimidate (64) is prepared from aniline and triethyl orthoformate by an acid-catalyzed reaction and rearranged to N-ethylformanilide (65) in the presence of acids, it is possible to prepare the anilide 65 from aniline and triethyl orthoformate in a single step without isolating the imidate. The anilide 65 is readily hydrolyzed to N-ethylaniline in high yield. Roberts has suggested these reactions as a practical synthesis of the monoalkylanilines.[72]

Cramer and Hennrich studied the rearrangement of trichloroacetimidates and found that boron trifluoride is an excellent catalyst for the reaction.[73] The methyl ester 66 gave the amide 67 in 91% yield, while the corresponding ethyl ester rearranged in 96% yield. The benzyl ester

$$CCl_3C \overset{\underset{\displaystyle OCH_3}{|}}{=} NH \qquad\qquad CCl_3C \overset{\underset{\displaystyle \parallel}{O}}{-} NHCH_3$$

$$\underset{66}{} \qquad\qquad\qquad \underset{67}{}$$

gave only 15% of N-benzyltrichloroacetamide, the remainder being trichloroacetamide.[73]

[72] Roberts and Vogt, J. Am. Chem. Soc., 78, 4778 (1956).

[73] Cramer and Hennrich, Chem. Ber., 94, 976 (1961).

Although boron trifluoride and sulfuric acid can be used to catalyze the rearrangements of imidates, acids which furnish good nucleophiles cannot. When imidate hydrochlorides are heated, cleavage occurs instead of rearrangement. This reaction, known as the Pinner fission,

$$\underset{\substack{|\\RC=NH\cdot HCl}}{\overset{OR'}{}} \rightarrow \underset{\substack{\|\\RCNH_2}}{\overset{O}{}} + R'Cl$$
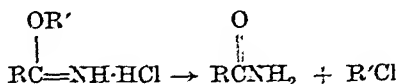
has been studied by McElvain[74] and Cramer.[75] It involves nucleophilic attack by chloride ion on the protonated imidate.

Aryl imidates do not undergo the Pinner fission. Phenyl N-phenyl-benzimidate on heating with hydrogen chloride yielded phenol and N-phenylbenzimidoyl chloride.[76]

$$\underset{\substack{|\\C_6H_5C=NC_6H_5}}{\overset{OC_6H_5}{}} \xrightarrow{\text{HCl}} C_6H_5OH + C_6H_5C(Cl)=NC_6H_5$$
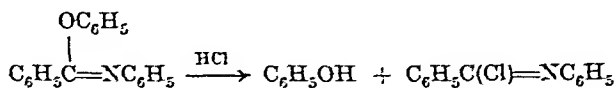
Thermal Rearrangement of Alkyl Imidates

There have been several reports of the thermal isomerization of alkyl imidates, but, except for the methyl, benzyl, and allyl derivatives which will be considered later, when the reactions were re-examined it was found that the pure imidates did not rearrange. Two examples will suffice.

The imidate 68 was reported to rearrange to the amide 69 in 35% yield on heating for 6 hours at 270–280°.[77] Lander, in the first careful study of the thermal behavior of alkyl imidates, showed that the carefully purified imidate 68 underwent negligible isomerization after 8 hours at 250–270° and 3 hours at 300°.[65] Similarly the imidate 70 was reported to

$$\underset{\substack{|\\C_6H_5C=NC_6H_5\\ \textbf{68}}}{\overset{OCH_3}{}} \qquad \underset{\substack{\\C_6H_5CN(CH_3)C_6H_5\\ \textbf{69}}}{\overset{O}{}}$$

rearrange to the lactam 71 in 85% yield after 2 hours at 180–250°.[69] Later it was shown that the rearrangement of 70 was due to the presence of an impurity, probably diethyl sulfate.[70]

When the alkyl group in an alkyl imidate can undergo elimination, this, rather than isomerization, appears to be the normal pyrolysis pattern. Thus the ethyl and sec-butyl analogs of 68 furnished benzanilide and ethylene[68] and 2-butene,[9] respectively, and the imidate 70 yielded caprolactam and ethylene.[70] Pyrolysis of alkyl imidates has been suggested as a way of dehydrating secondary alcohols.[9]

Since elimination cannot occur, pyrolysis of methyl imidates can apparently give rearrangement products; e.g., the methyl imidate 68 gave the amide 69 in 25% yield when heated at 300–330°,[3] and conversion of 72 to the amides 73 occurred in 20–40% yields at about 300°.[78]
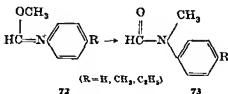
The temperatures needed are higher than those generally required for the Chapman rearrangement of aryl imidates, and the yields are lower. The reaction has been shown to be intermolecular, in contrast to the Chapman rearrangement which is intramolecular.[78] Wiberg[9] believes that the thermal rearrangement of alkyl imidates is a free radical process.

Benzyl imidates, like the methyl compounds, cannot undergo the elimination reaction and would be expected to rearrange. The thermal conversion shown in the accompanying equation has been reported without reference to reaction conditions.[79]
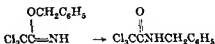
The cyclic benzyl imidate 74 furnished the isoindole derivative 75 in 70% yield when heated for 2 hours at 300°.[80] On steric grounds the four-membered transition state of the Chapman rearrangement cannot exist,

[78] Wiberg, Shryne, and Kintner, *J. Am. Chem. Soc.*, **79**, 3160 (1957).
[79] Cramer, Pawelzik, and Kupper, *Angew. Chem.*, **68**, 649 (1956).
[80] Stirling. *J. Chem. Soc.*, **1960**, 255.

and it seems likely that the reaction proceeds via the intermediate diradical shown in the formulation.   Attempts to rearrange the analogous N-benzyl and N-cyclohexyl compounds at 300° failed.[80]

74

75
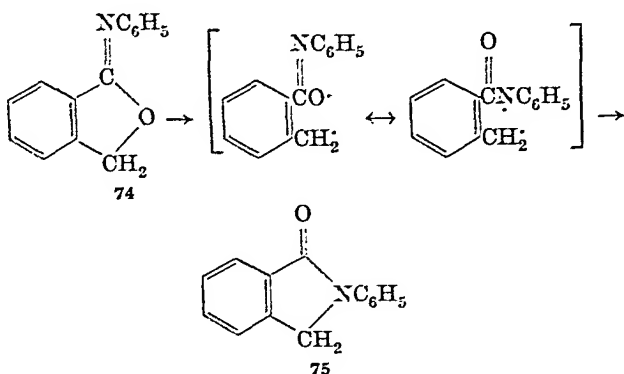
Allyl imidates undergo thermal rearrangement more readily than the methyl or benzyl derivatives.   The reaction was first observed by Mumm and Möller[81] with the allyl imidate 76.

76
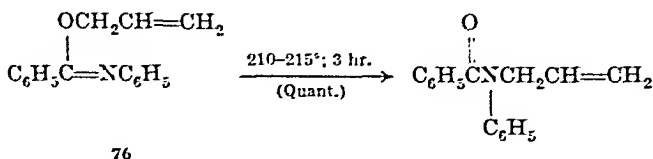
This rearrangement could conceivably occur either via a four-membered or a six-membered transition state.   Mumm showed that the latter was the route indicating that the reaction resembles the Claisen rather than the Chapman rearrangement.   The imidate 77 gave the amide 79 stereospecifically, presumably via 78.[81]

77

78

79
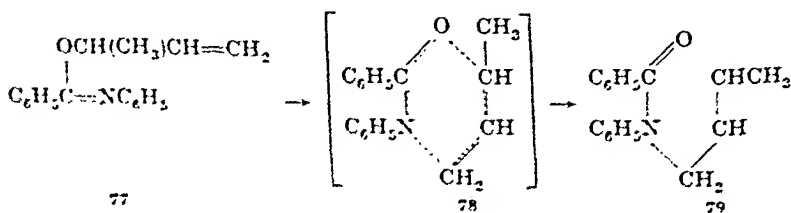
Similarly, the imidate 80 yielded the amide 81.[81] If the Chapman mechanism had been operative, the expected product would be 79.

OCH$_2$CH=CHR

C$_6$H$_5$C=NC$_6$H$_5$

O
‖
CH(R)CH=CH$_2$
|
C$_6$H$_5$C—N
|
C$_6$H$_5$

80 (R=CH$_3$)   81 (R=CH$_3$)
82 (R=C$_2$H$_5$)   83 (R=C$_2$H$_5$)
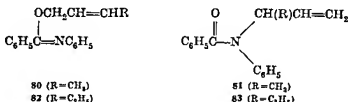
The higher homolog 82 rearranged at 235° to furnish 83.[82] When either 82 or 83 was heated for 3 hours at 290°, a different product, 85, was obtained.[82] Evidently this resulted via a six-membered transition state 84 strictly analogous to that postulated for the Claisen rearrangement.*

85

Earlier the rearrangement of the terminally substituted imidate 86 at 225–260° was shown to result in a 75% conversion to 87. The possible intermediate 89 (corresponding to 83) was not obtained.[81]

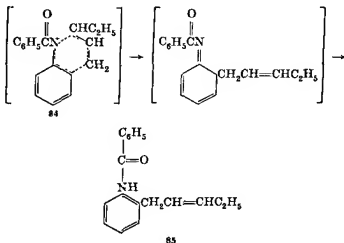[81] Lauer and Benton, *J. Org. Chem.*, 24, 804 (1959).

* Recently the conversion of N-allyl-1-naphthylamine to 2-allyl-1-naphthylamine was claimed to be the first example of a Claisen rearrangement from a nitrogen atom.[83] Apparently the earlier work was overlooked.

[82] Marcinkiewicz, Green, and Mamalis, *Tetrahedron*, 14, 208 (1961).

[83] Lauer and Lockwood, *J. Am. Chem. Soc.*, 76, 3974 (1954).

86 (R=H)
88 (R=CH₃)   87
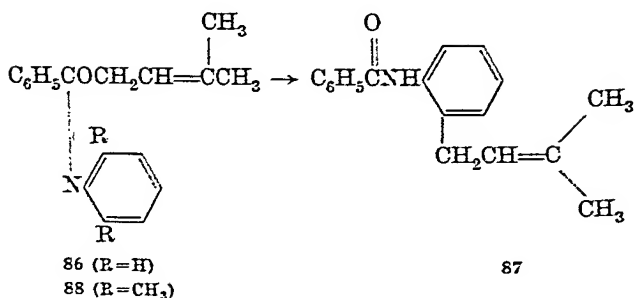
The analogous *o,o-'*disubstituted imidate **88**, which could not lead to
aryl substitution, gave only benz-2,6-dimethylanilide on pyrolysis; **90**
was not obtained.[82] Lauer therefore concluded that the rearrangement
of **86** to **87** is probably not a two-step reaction and does not proceed via
89. Instead, a one-step mechanism proceeding via the transition state
91 was postulated.[82,84] However, the steric effect exerted by the two
ortho methyl groups in **88** could conceivably prevent formation of **90** even
if **89** were formed normally. Furthermore, it seems unlikely that **86**

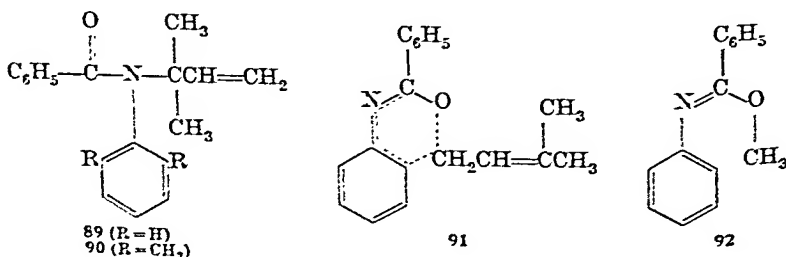89 (R=H)   91   92
90 (R=CH₃)

would rearrange readily via **91** at 260° since the imidate **92** is stable at
300°.[63] The mechanism of this change is doubtful at present.
   Although the preceding thermal reactions proceed stereospecifically and
intramolecularly, the acid-catalyzed rearrangment of allyl imidates gives
mixtures, undoubtedly by way of an ionic mechanism. Roberts and
Hussein found that the thermal rearrangement of the imidate **93**, for
example, gave **94**.[85] In contrast, when the same imidate, **93**, was heated

93   94
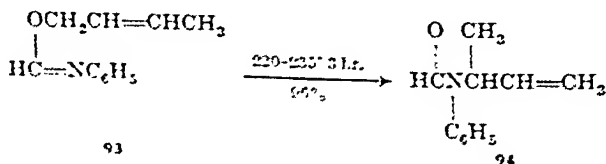
with concentrated sulfuric acid, reaction began at 100° and a mixture of many components, including 94 and its allylic isomer, resulted.[85]

Rearrangements of Acyl Imidates

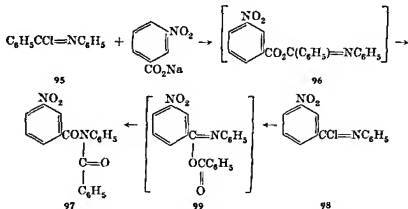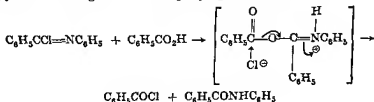The Mumm rearrangement, which apparently involves the rearrangement of acyl imidates (imino anhydrides), was discovered before the Chapman rearrangement. When N-phenylbenzimidoyl chloride (95) was treated with sodium m-nitrobenzoate, the expected product 96 was not isolated; instead, the diacylaniline 97 was obtained.[1] N-Phenyl-m-

$$C_6H_5CCl=NC_6H_5 \; + \; \underset{CO_2Na}{\underset{|}{\overset{NO_2}{\overset{|}{\bigcirc}}}} \; \longrightarrow \; \left[\underset{96}{\overset{NO_2}{\bigcirc} CO_2C(C_6H_5)=NC_6H_5} \right] \longrightarrow$$

nitrobenzimidoyl chloride 98 and sodium benzoate also gave 97, presumably via the acyl imidate 99.[1] In no case could an O-acyl compound be isolated. As a result of this failure Mumm was led to study the behavior of a stable aryl imidate and, as a result, discovered the reaction now known as the Chapman rearrangement.

Recently Cramer and Baer attempted to prepare acyl imidates from the reaction of imidoyl chlorides, carboxylic acids, and triethylamine.[86] As before, no intermediates could be isolated; the imides were obtained in almost quantitative yield. When the triethylamine was omitted, a reaction analogous to the Pinner fission resulted, and acyl halides and amides were isolated. For example, benzoyl chloride was obtained in *90% yield according to the accompanying formulation* [85]

$$C_6H_5CCl=NC_6H_5 \; + \; C_6H_5CO_2H \; \longrightarrow \; \left[\underset{Cl^{\ominus}}{C_6H_5C} \overset{O}{\underset{}{\overset{\|}{\cdots}}} C \underset{C_6H_5}{\overset{O}{\underset{\|}{\cdots}}} \overset{H}{\underset{}{N}} C_6H_5 \right] \longrightarrow$$

$$C_6H_5COCl \; + \; C_6H_5CONHC_6H_5$$

Stevens and Munk[87] prepared imides (102) from diphenylketene *p*-tolylimine (100) and carboxylic acids, but the anticipated acyl imidates (101) were not isolated. The authors suggested that the reaction proceeded via a four-membered transition state; if so, it is mechanistically analogous to the Chapman rearrangement. The same authors also briefly mention other related reactions which involve acyl migration from oxygen to nitrogen, probably via four-membered transition states.[87] Recently a compound believed to be a stable acyl imidate (103) has been prepared.[88]
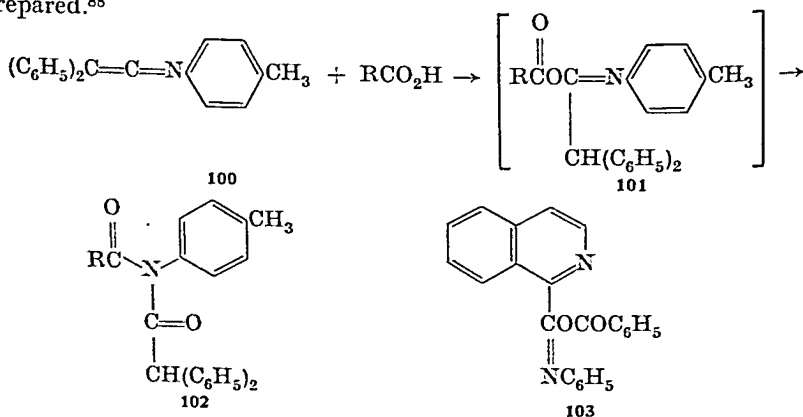
Miscellaneous Rearrangements

The conversion of the chloroethyl imidate 104 to the amide 105 takes place at 130°.[89] The low temperature indicates that neither the normal Chapman rearrangment nor a dissociation into radicals occurs. Most likely the reaction proceeds via internal displacement of halogen to give the five-membered intermediate shown. Nucleophilic attack of chloride ion would then give the amide.
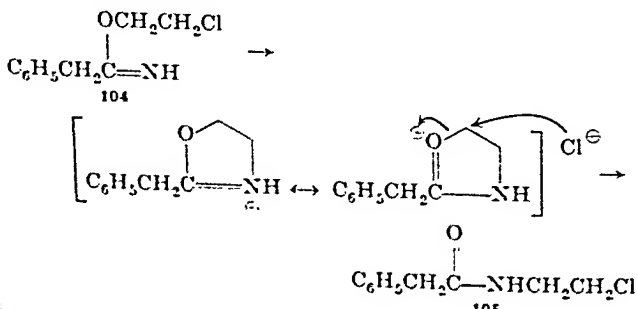
The quinazoline **106** is converted to the tricyclic compound **108** upon distillation at 211°.[90] It has been suggested that the reaction proceeds by way of **107**. The mechanism for the formation of **107** is uncertain. A route analogous to that suggested for the rearrangement of **104** seems unlikely, since this would involve formation of an ion pair containing the diethylamide anion.
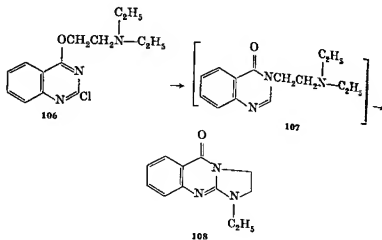
The cyclic imine 111 has been converted to the urethan 112 by heating with lithium chloride.[92]   The reaction probably proceeds by halide ion attack to give the intermediate shown, which then closes in the alternative sense to the final product.

$$C_6H_5N= \overset{O}{\underset{O}{\big\langle}} \quad \overset{Cl^\ominus}{} \quad \rightarrow$$

111

$$\left[\begin{array}{c} \overset{O^\ominus}{\underset{|}{C_6H_5N=C}}-OCH_2CH_2Cl \leftrightarrow C_6H_5\overset{\ominus}{N}- \qu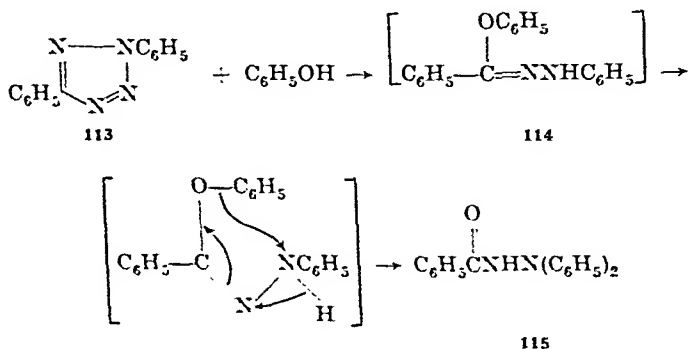ad C=O \\ H_2C \quad O \\ Cl \quad CH_2 \end{array} \right] \rightarrow C_6H_5N-\overset{}{\underset{O}{\big\rangle}}=O$$

112
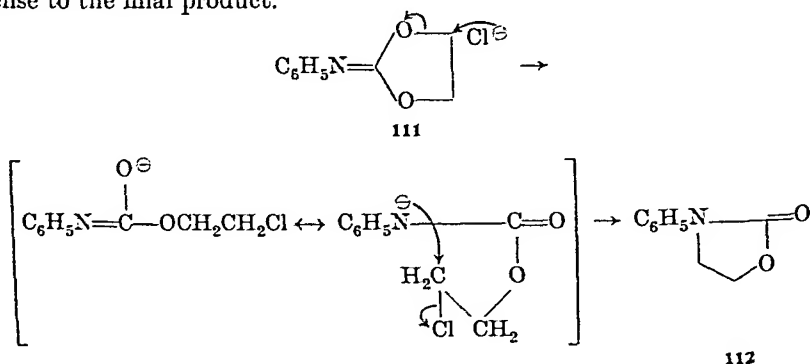
The tetrazole 113 is converted to the hydrazide 115 in refluxing phenol.[93] The reaction presumably proceeded through the intermediacy of 114 which, Huisgen suggested, rearranges via a five-membered cyclic transition state.   This route, which would involve a hydride shift, supposedly took precedence over the Chapman rearrangement because of the larger ring involved in the transition state.[93]

$$\underset{C_6H_5}{\overset{N-NC_6H_5}{\big|\big|}}\underset{N=N}{\big|} \;\div\; C_6H_5OH \rightarrow \left[\underset{C_6H_5-C=NNHC_6H_5}{\overset{OC_6H_5}{|}} \right] \rightarrow$$

113   **114**

$$\left[C_6H_5-C \underset{N}{\overset{O-C_6H_5}{\big\diagup}} \overset{NC_6H_5}{\underset{H}{\big\diagdown}} \right] \rightarrow C_6H_5\overset{O}{\overset{||}{C}}NHN(C_6H_5)_2$$

115

As a natural extension of his study of aryl imidates, Chapman examined sulfur analogs such as 116.   At 280–290° for 2 hours, isomerization to 117 took place only to a small extent.   At 320°, both 116 and 117 gave a mixture containing diphenyl sulfide, benzonitrile, thiophenol, and the

benzthiazole 118. Since both reactants gave the same mixture, Chapman suggested that the rearrangement is reversible.[94]

$$C_6H_5C \cdot NC_6H_5 \quad \rightarrow \quad C_6H_5C \cdot N(C_6H_5)_2$$

116   117   118
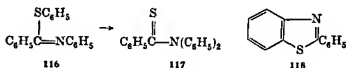
In a series of papers Chapman reported on the analogous amidines.[16-18,95,96] Here, as expected, the rearrangement was shown to be reversible. Either 119 or 120 on heating gave the equilibrium mixture shown in the equation.[95]

119
(60-65%)

120
(35-40%)
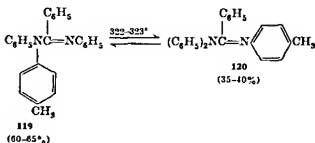
Chapman also heated a mixture of triphenylbenzamidine and tri-*p*-tolylbenzamidine. Since the mixture after heating had the same melting point as before, it was concluded that no mixed amidines had been formed and that the reaction is intramolecular.[16] The mechanism is probably completely analogous to that of the Chapman imidate rearrangement. In the amidine rearrangement, if all three N-aryl groups are different, an equilibrium mixture of three components should result, but, if the three aryl groups are identical, aryl migration leads only to starting material.

Chapman[3] believed that the thermal rearrangement of aryl imidates was reversible, but, since heating aroyldiphenylamines failed to produce detectable amounts of imidates, he concluded that the equilibrium lies so far to the amide side that reversibility is not appreciable. No examples of the reverse reaction have been reported thus far.
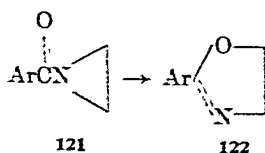
The thermal rearrangement of aroylaziridines such as 121 to cyclic imidates 122 has been reported. Since this reaction is readily catalyzed

[94] Chapman, J. Chem. Soc., 1926, 2296.
[95] Chapman, J. Chem. Soc., 1929, 2133.
[96] Chapman and Perrott, J. Chem. Soc., 1930, 2462.

by acids or nucleophiles (iodide ion), it is uncertain whether the
uncatalyzed reaction really occurs.[97]

EXPERIMENTAL CONDITIONS

N-Arylbenzimidoyl Chlorides

The conversion of amides to imidoyl chlorides has generally been
carried out by heating with an equimolecular amount of phosphorus
pentachloride, usually without solvent.[98,99] The reaction often begins
spontaneously at room temperature, and, after removal of the resulting
phosphorus oxychloride, the product may be isolated either by crystal-
lization or distillation, the latter being preferred for low-melting solids.
Frequently, after removal of the phosphorus oxychloride, the crude
product is used directly without purification.[12,20,26,44] Occasionally,
carbon tetrachloride[29] or toluene[100] has been used as a solvent for the
reaction.

Thionyl chloride has been used less frequently but has given equally
good results,[52,101,102] as exemplified by the preparation of N-phenyl-
benzimidoyl chloride in 95% or better yield.[52,101] Phosphorus oxy-
chloride has been used for the preparation of N-(9-phenanthryl)benzim-
idoyl chloride, but no yield was given.[48] The authors of this chapter
have found this reagent distinctly inferior to phosphorus pentachloride or
thionyl chloride in the preparation of N-(4-fluorophenyl)benzimidoyl
chloride.[13]

Aryl N-Arylbenzimidates

Phenyl N-phenylbenzimidate was first prepared by Hantzsch from a
suspension of sodium phenoxide and N-phenylbenzimidoyl chloride in
ether.[103] Since then, almost all imidates have been synthesized by
treating the phenol with sodium ethoxide in ethanol and then adding

the imidoyl chloride in ether.[9,15,104] The reaction, which is often run under nitrogen, takes place readily at room temperature. The imidates are usually crystalline and are easily isolated, generally in high yield. Commercial sodium methoxide in methanol gives equally good results.[35,44] A slight excess of the phenol is often used.

Dioxane[23] and ethyl acetate[13] may be used instead of ether for dissolving the chlorides. Cookson has also prepared imidates from phenols and imidoyl chlorides in pyridine, the last reagent serving both as base and solvent.[23] Easson has treated sodium salts of cyanophenols in pyridine with either the molten imidoyl chloride or the chloride in pyridine.[29] Good results were also obtained from phenols, chlorides, and triethylamine in ether or dioxane.[29]

N-Aroyldiarylamines

The Chapman rearrangement has usually been carried out by heating the imidate without a solvent. In most cases, temperatures of 250–300° are used. However, imidates derived from acidic phenols will rearrange at lower temperatures, o-nitrophenyl N-phenylbenzimidate being converted to N-benzoyl-o-nitrodiphenylamine in 1 hour at 165°.[3] Usually heating periods of less than 3 hours are sufficient. Imidates derived from methyl salicylate are usually rearranged by heating at about 280° for about 10 minutes.[15] The reaction is exothermic and the internal temperature may go above 300° if a large quantity of imidate is pyrolyzed. In experiments where temperature control is not critical, the vessel used for the rearrangement may be heated by a Wood's metal bath. If more careful control is desired, a constant external temperature may be held by heating the vessel with the vapors of a high-boiling material such as bibenzyl.[35]

In a few reactions, solvents have been used. Cookson was unable to obtain crystalline rearrangement products by heating certain iodine-containing imidates without solvent. However, when nitrobenzene (b.p. 209°), diphenyl ether (b.p. 259°), biphenyl (b.p. 254°), or o-dichlorobenzene (b.p. 180°) was used as solvent, the desired product could be obtained in reasonable yield in some cases.[23] Dowtherm was used successfully as the solvent for rearranging many cyanoimidates.[29] Imidates derived from o-nitrophenol have been rearranged in boiling anisole (b.p. 155°) and even pyridine (115°).[29] In Wiberg's[8] kinetic study of the Chapman rearrangement, diphenyl ether was used as the solvent.

[104] Chapman, *J. Chem. Soc.*, **121**, 1676 (1922).

Hydrolysis of Rearrangement Products

Hydrolysis of the rearrangement products was first carried out by Chapman who heated under reflux a mixture of 10 g. of N-benzoyl-diarylamine, 50 ml. of 50% aqueous potassium hydroxide, and 125 ml. of ethanol for 2 hours.[4]   Essentially the same method of basic hydrolysis has been used in almost all cases reported, the only changes being in the relative proportions of reagents.   Sodium hydroxide in aqueous ethylene glycol has been employed to hydrolyze a series of cyano-substituted N-benzoylamines.[29]

Hydrolysis of the rearrangement products derived from methyl salicylate to derivatives of diphenylamine-2-carboxylic acids is also carried out with excess base in aqueous ethanol[15] or aqueous dioxane.[44] Essentially the same procedure, but with equimolar amounts of alkali and N-benzoyl ester, is used for the partial hydrolysis of these compounds to the N-benzoyl acids.[15]

Acridones

Although acridones have been prepared directly from benzimidates and from derivatives of N-benzoyldiphenylamine-2-carboxylic acid, very few examples have been reported. Because detailed experimental directions have rarely been given, little can be said about experimental conditions.   For the preparation of acridones via other routes, the reader should consult Acheson.[54]

at 110–116°/0.15 mm., through a short Vigreux column. Rapid distillation is necessary to prevent the yellow distillate from crystallizing in the apparatus. The yield is 41.6 g. (98%) of almost white solid, m.p. 58–63°.

Phosphorus Pentachloride. (a) A mixture of 10.8 g. (0.05 mole) of 4'-fluorobenzanilide and 10.4 g. (0.05 mole) of phosphorus pentachloride is heated under reflux for 1 hour. After removal of the phosphorus oxychloride at water pump vacuum, the product is distilled using an oil pump to give 10.6 g. (91%) of product.

(b) The phosphorus oxychloride is removed as described above, and the residue is crystallized from hexane to give 9.3 g. (79%) of white solid. The product is less pure than the distilled material and gives a cloudy melt. Recrystallization from hexane gives the product, m.p. 62–65°, in 54% yield.

o-Carbomethoxyphenyl N-Phenylbenzimidate.[15,36] A 250-ml. three-necked flask, equipped with a Hershberg stirrer and a delivery tube arranged so that a slow stream of nitrogen passes through the liquid, is charged with 100 ml. of absolute ethanol to which is added 1.9 g. (0.083 g. atom) of sodium. After the conversion to sodium ethoxide is complete, the solution is cooled to room temperature and a solution of 15.2 g. (0.10 mole) of methyl salicylate in 15 ml. of absolute ethanol is added quickly. A solution of 17.3 g. (0.08 mole) of N-phenylbenzimidoyl chloride in 30 ml. of dry diethyl ether is then added within a few minutes. The reaction mixture is stirred overnight at room temperature under nitrogen, most of the solvent is removed in vacuum, and the residue is mixed with water. The insoluble solid is recrystallized from absolute ethanol to give 23.5 g. (89%) of white prisms, m.p. 114–117° Ultraviolet (ethanol): λ_{max} 227 mμ (ϵ 27,345) and 275 mμ (ϵ 11,720). Infrared (KBr): 5.82 μ, 6 00 μ.

p-Fluorophenyl N-(*p*-Fluorophenyl)benzimidate.[12] In a 250-ml. flask equipped with a magnetic stirrer, 6 5 g. (0.12 mole) of sodium methoxide (Matheson, Coleman and Bell) is dissolved in 125 ml. of methanol and the solution is cooled to about 20°. Then 13.4 g. (0 12 mole) of *p*-fluorophenol (Aldrich) is added all at once   In the course of the next few minutes a solution of 23.4 g. (0.10 mole) of N-(*p*-fluorophenyl)benzimidoyl chloride in 50 ml. of dry ethyl acetate is added. The mixture turns cloudy at once, and the temperature rises from 25° to 37°.

The mixture is stirred for 3 hours, after which time the solvent is removed in vacuum. Water is added and the white insoluble solid filtered and washed with water. After air-drying, 27 g. (m.p. 99–106°) of the product is obtained which upon recrystallization from absolute ethanol gives 23.5 g. (83%) of material which melts at 105–109°. Ultraviolet

(ethanol): λ_{max} 220 mμ (shoulder, ϵ 16,300), 229 mμ (shoulder, ϵ 15,500), 266 mμ (ϵ 6560), and 272 mμ (ϵ 6500). Infrared (KBr): 6.08 μ.

o-Carbomethoxyphenyl N-[(*o*-Carbomethoxymethyl)phenyl]-benzimidate.[44] N[(*o*-Carbomethoxymethyl)phenyl]benzimidoyl chloride is prepared by mixing 56.5 g. (0.21 mole) of methyl *o*-benzamidophenyl-acetate[44] and 43.7 g. (0.21 mole) of phosphorus pentachloride in a 500-ml. flask. The reaction begins spontaneously at room temperature, and hydrogen chloride evolution occurs with extensive foaming. The mixture is then heated gently on the steam bath until the gas evolution virtually ceases. The phosphorus oxychloride is removed in vacuum below 50°, toluene is added, and the solvent once again removed in vacuum to leave the crude imidoyl chloride as a dark red oil, which is used without purification.

Meanwhile a solution of 12.4 g. (0.23 mole) of sodium methoxide in 200 ml. of methanol is flushed with nitrogen and cooled with an ice bath. To this is added with stirring a solution of 35.0 g. (0.23 mole) of methyl salicylate in 50 ml. of methanol. The crude imidoyl chloride in 65 ml. of anhydrous diethyl ether is then added during 5 minutes. The ice bath is removed and the cloudy tan mixture stirred for 3 hours at room temperature, after which water is added and the product taken up in ether. The red extracts are dried and the solvent is removed to give a dark oil which solidifies and is crystallized from methanol-hexane to furnish 59.2 g. (70%) of yellow prisms, m.p. 60–64°. This material is pure enough to be used directly in the Chapman rearrangement. Two recrystallizations from methanol give a white solid, m.p. 62–65°. Ultraviolet (ethanol): λ_{max} 228 mμ (ϵ 24,000), 278 mμ (ϵ 5400). Infrared (KBr): 5.80 μ and 5.97 μ.

N-Benzoyldiphenylamine.[2,12] Five grams of phenyl N-phenylbenz-imidate is placed in a small pear-shaped flask carrying a thermometer that dips into the solid. The flask is immersed for an hour in a Wood's metal bath held at 312–315°. The melt, whose temperature during the heating is 305–310°, crystallizes on cooling. The solid is taken up in warm absolute ethanol. After cooling, filtering, washing the tan solid with ethanol and air-drying, 4.6 g. (92%) of product, m.p. 177–181° is obtained. One recrystallization from absolute ethanol (charcoal) gives 4.0 g. (80%) of white needles, m.p. 178–182°. Ultraviolet (ethanol): λ_{max} 235 mμ (shoulder ϵ 13,100), 271 mμ (ϵ 7220). Infrared (KBr): 6.09 μ.

Methyl N-Benzoyldiphenylamine-2-carboxylate.[15,36] A 125-ml. Erlenmeyer flask equipped with a thermometer and containing 30 g. of *o*-carbomethoxyphenyl N-phenylbenzimidate is heated in a Wood's metal bath. When the bath temperature reaches 240°, an exothermic reaction begins and the internal temperature quickly rises to 260°. After about

a minute, the internal temperature begins to drop. The bath is then heated for 10 minutes at 280°. The dark melt is cooled somewhat, then poured into 160 ml. of hot absolute ethanol. On cooling, the product crystallizes to give 24.5 g. (82%) of slightly yellow solid, m.p. 133–135.5°. Ultraviolet (ethanol): inflection at 273 mμ, ε 6830. Infrared (KBr): 5.80 μ, 6.04 μ.

Methyl 2,6-Diiodo-4'-methoxydiphenylamine-4-carboxylate.[23] A solution of 4.0 g. of 4-carbomethoxy-2,6-diiodophenyl-N-p-methoxyphenylbenzimidate[23] in 12 ml. of o-dichlorobenzene is heated under reflux for 80 minutes. Petroleum ether (b.p. 100–120°) is added until crystals begin to separate from the boiling solution. On cooling, 3.8 g. (95%) of the product is obtained. After recrystallization from toluene-petroleum ether (b.p. 100–120°), the pure material melts at 205°.

4-Fluorodiphenylamine.[13] A mixture of 10.9 g. (0.037 mole) of N-benzoyl-4-fluorodiphenylamine, 30 g. of potassium hydroxide in 30 ml. of water, and 125 ml. of ethanol is heated under reflux for 2 hours. Water is added and the mixture is concentrated in vacuum in order to remove most of the ethanol. The cloudy mixture is then extracted three times with diethyl ether and the extracts dried. Removal of the solvent gives a dark red oil which is vacuum-distilled with a small Vigreux column. The product is obtained as a yellow liquid, b.p. 78–80°/0.01 mm., which crystallizes on cooling, m.p. 33.5–35.5°; yield 5.9 g. (85%). Ultraviolet (ethanol): λ_{max} 241 mμ (shoulder ε 3860), 281 mμ (ε 18,600). Infrared (chloroform): 2.99 μ.

N-Benzoyldiphenylamine-2-carboxylic Acid.[15] A mixture of 24.5 g. (0.074 mole) of methyl N-benzoyldiphenylamine-2-carboxylate, 3.8 g. (0.070 mole) of sodium methoxide, 180 ml. of ethanol, and 75 ml. of water is heated under reflux for 2 hours. The resulting pale orange alkaline solution is diluted with water, washed once with ether, and acidified with excess hydrochloric acid. The precipitate is filtered and washed with water. After drying for 1 hour at 95°, 21 g. of crude product is obtained which, after recrystallization from acetone-pentane, affords white crystals, m.p. 190–193°. The yield is 18.9 g. (80% based on N-benzoyl ester).

Diphenylamine-2-carboxylic Acid.[15,36] Two grams (0.006 mole) of methyl N-benzoyldiphenylamine-2-carboxylate is treated with a solution of 8 g. of potassium hydroxide in 20 ml. of water and 60 ml. of methanol The mixture is heated under reflux for 2.5 hours, diluted with water, and a trace of insoluble material is removed by filtration. Excess hydrochloric acid is then added and the mixture is heated to boiling to dissolve benzoic acid. The insoluble product is filtered hot and washed with

boiling water to give a white powder, m.p. 169–179°. One recrystallization from ethanol-water gives 1.0 g. (77%) of product, m.p. 188.5–191°. Ultraviolet (ethanol): λ_{max} 220 mμ (ϵ 21,800), 287 mμ (ϵ 13,900), 348 mμ (ϵ 6500). Infrared (KBr): 3.00 μ, 6.02 μ.

2,4,7-Tribromoacridone.[105] (a) N-Benzoyl-4,4′,6-tribromodiphenylamine-2-carboxylic acid (5.0 g., 0.009 mole)[15,105] is heated at 300–350° for a few minutes. The material is boiled with a little aqueous sodium hydroxide, then with water. Recrystallization from m-cresol furnishes 2.17 g. (56%) of pale yellow needles, m.p. >340°.

(b) A mixture of 1.0 g. (0.0018 mole) of methyl N-benzoyl-4,4′,6-tribromodiphenylamine-2-carboxylate[15,105] and 2.10 ml. of concentrated sulfuric acid is heated at 160–200° for about a minute. On cooling, the product crystallizes to give 0.66 g. (87%) of the acridone.

5-Methyl-1,2-benzacridone.[48] 2-Carbomethoxy-6-methylphenyl N-β-naphthylbenzimidate[48] (22 g., 0.056 mole) is heated at 360° under nitrogen for 0.5 hour. Methyl benzoate is formed and boils away. The residual solid is cooled, washed with benzene, and recrystallized from nitrobenzene to give 5.5 g. (38%) of yellow needles, m.p. 264–265°.

TABULAR SURVEY

In listing benzimidates

$$\begin{array}{c} OR \\ | \\ R''\!\!-\!\!C\!\!=\!\!NR' \end{array}$$
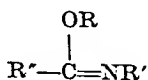
compounds with R = R′ = phenyl are named first. Next, derivatives of phenol (R = phenyl, R′ varies) are listed, and, last, compounds where R varies are listed. Within each group, monohalo derivatives are named first, followed by nitro-, hydroxy-, methoxy-, and alkyl-substituted compounds. Imidates with one carbonyl-containing substituent are named next. Finally, compounds with more than one substituent on the key radical are listed, followed by imidates derived from polycyclic and heterocyclic phenols.

In the tables a dash (—) indicates that a compound has been prepared but no yield was given. Omission of both the yield and the dash shows that the reaction leading to the compound in question was not attempted.

The literature coverage includes July, 1963.

All references to a particular listing are located in the last column. When multiple references occur, individual citations appear in parentheses under the appropriate heading.

[105] Acheson and Robinson, *J. Chem. Soc.*, **1953**, 232.

TABLE I

ARYL N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

Aryl N-Arylbenzimidate

$$R-\overset{OR'}{\underset{}{C}}=NR''$$

OR

$$R''-N-C-$$ N-Aroyldiarylamine

R	R'	R''	Aryl N-Arylbenzimidate Yield, % (Ref.)	Conditions for Rearrangement (ref.) (2)	N-Aroyldiarylamine Yield, % (Ref.)	Diarylamine R₂NH Yield, % (Ref.)	References
C₆H₅	C₆H₅	C₆H₅	64 (9)	240°; 1 hr. (1) / 270–300°; 2 hr. (3)	Complete transformation (2)		1–3, 9
	C₆H₅	o-ClC₆H₄	—	206°; 1.5 hr. (3)	71†		3
	C₆H₅	p-ClC₆H₄	—	270°; 1.5 hr.	63†		3
	C₆H₅	o-O₂NC₆H₄	—	270°; 1.5 hr.	62†		3
	C₆H₅	p-O₂NC₆H₄	—		*		3
	C₆H₅	p-CH₃OC₆H₄	—	270°; 1.5 hr.	49‡		3
	C₆H₅	p-FC₆H₄	54	267°; 1.5 hr.	85†		3
	C₆H₅	o-ClC₆H₄	—	270°; 1.5 hr.	<55†		13
	C₆H₅	o-CH₃C₆H₄	—	305–315°; 1 hr.	91	85	3, 20
	C₆H₅	p-O₂NC₆H₄	—	270°; 1.5 hr.	39†		3
	C₆H₅	p-CH₃OC₆H₄	65	270°; 1.5 hr. (3)	49†		25
	C₆H₅	p-CH₃C₆H₄	28	270°; 1.5 hr.	61†		24
	C₆H₅	p-CH₃OC₆H₄	88	200°; 2 hr.	*		27
	C₆H₅	2,4-Cl₂C₆H₃	—	290–300°; 2 hr.	85†	—(26)	
	C₆H₅	3,5-Cl₂C₆H₃	—	200°; 2 hr.	—	Satisfactory	
	C₆H₅	2,4,6-Cl₃C₆H₂	—	300–310°; 2 hr.	High	68	
	C₆H₅	p-IC₆H₄	—	270°; 1.5 hr.	34‡	84‡	17
	C₆H₅	C₆H₅	—	270°; 1.5 hr.	<17†		
	C₆H₅	C₆H₅	—	270°; 1.5 hr.	63†		

Note. References 108 and 107 are on p. 51.

* The rearrangement was carried out as part of a kinetic study (ref. 9). The product was not isolated.
† This represents percent conversion and percent yield during a kinetic study (ref. 3).
‡ The reaction was unsuccessful and the yield was not given.
§ For preparative means, the rearrangement was satisfactory at the temperature indicated (ref. 3).
|| The yield is based on imidate.

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TABLE I—Continued

ARYL N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

R	R'	R''	Yield, % (Ref.)	Conditions for Rearrangement (Ref.)	N-Aroyldiarylamine Yield, % (Ref.)	Diarylamino RNHR' Yield, % (Ref.)	References
p-ClC6H4	C6H5	C6H5	55	305–310°; 1 hr.	85	85	13
p-BrC6H4	p-BrC6H4	C6H5	62	280°; 18 hr.	80	08	12
o-ClC6H4	C6H5	C6H5	37 (9)	270–280°; 1 hr. (2)	91•†		2, 3, 9
o-CH3C6H4	o-CH3C6H4	C6H5	—	255°; 1.5 hr. (3)	—	+	18
o-CH3C6H4	C6H5	C6H5	—	200°; 2 hr.	—		10
m-ClC6H4	C6H5	C6H5	—	255°; 1.5 hr.	84†		3
m-ClC6H4	o-CH3C6H4	C6H5	—	200°; 2 hr.	—		10
o-ClC6H4	o-CH3C6H4	C6H5	—	200°; 2 hr.	—		10
p-ClC6H4	C6H5	C6H5	67 (9)	280–290°; 2 hr. (2)	92•†		2, 3, 9
o-ClC6H4	o-ClC6H4	C6H5	00	255°; 1.5 hr. (3)	71	71	15
m-ClC6H4	m-ClC6H4	C6H5	—	300°; 2 hr.	—	—	10
p-ClC6H4	p-ClC6H4	C6H5	94 (20)	200°; 2 hr.	78 (20)•	94 (20)	9, 10, 20
p-BrC6H4	p-BrC6H4	C6H5	40 (9)	—	75		15
2,4-Cl2C6H3	2,4-Cl2C6H3	C6H5	—	290–320°; 2.5 hr.	70	85	15
o-BrC6H4	o-BrC6H4	C6H5	00	250–270°; 2 hr.	90	87	21
C6H5	C6H5	C6H5	48	155–200°; 2.5 hr.	•		9
p-BrC6H4	p-BrC6H4	C6H5	51	255°	81	08	22
C6H5	C6H5	C6H5	75	270–290°; 2 hr.	40 (3)		1, 3, 9
o-O2NC6H4	o-O2NC6H4	C6H5	51 (9)	105°; 1 hr. (3)	‡ (1)		30
o-O2NC6H4	2-Br-4-CH3C6H3	C6H5	07	170–180°; 1 hr.	+		3, 9
m-HOC6H4	C6H5	C6H5	30 (9)	—	—		104
o-CH3OC6H4	C6H5	C6H5	57	200°; 1.5 hr.	74•†		3, 9
m-CH3OC6H4	C6H5	C6H5	20 (9)	200°; 1.5 hr.	55†		3
p-CH3OC6H4	C6H5	C6H5	08 (9)	200°; 1.5 hr.	41•†		3, 9
o-CH3C6H4	C6H5	C6H5	10	255°	•		9

o-ClC₆H₄	C₆H₅	—	—	PS (34)*	—	19
o-ClC₆H₄	C₆H₅	68	290–300°, 2 hr.	Isomerized	Satisfactory	15
o-ClC₆H₄	C₆H₅	38 (24); 60 (9)	240–300°, 2 hr.	completely	C.H	23
m-ClC₆H₄	C₆H₅	64	290–300°, 2 hr.	—	64 (25)	0, 24
p-ClC₆H₄	C₆H₅	56	290–300°, 2 hr. (24)	—	Satisfactory	23
p-ClC₆H₄	C₆H₅	—	240–300°, 2 hr.	—	—	23
o-CH₃C₆H₄	C₆H₅	15	275°	*		0
o-CH₃C₆H₄	C₆H₅	58	240–350°, 2 hr.	*		"
m-CH₃C₆H₄	C₆H₅	30	270–350°, 2 hr.	*		"
p-CH₃C₆H₄	C₆H₅	40	275°	40		"
p-CH₃C₆H₄	C₆H₅	67	255°	*		"
p-CH₃C₆H₄	C₆H₅	74	255°	*		"
p-CH₃C₆H₄	C₆H₅	<35	255°	*		"
p-CH₃C₆H₄	C₆H₅		230°, 2 hr.	*		"
o-CH₃C₆H₄	C₆H₅		300°	Almost quantitative		27
p-CH₃C₆H₄	C₆H₅		275°, 2.5 hr.	85		28
p-C₂H₅·CH₂·C₆H₄	C₆H₅		275°, 2.5 hr.	85		33
p-OBCC₆H₄	C₆H₅	35	270°, 40 min.	‡		33
		By hydrolysis of methyl ester		*		33
m·CH₃O·C₆H₄	C₆H₅	73 (25)	259–260°, 2 hr. (33)	81 (33)	73 (30)¶	33
p·ClC₆H₄	p·ClC₆H₄		300°, 2 hr. (25)	84 (29)		26, 33
p·CH₃C₆H₄	C₆H₅	67	277–300°	90	61¶	15
						33

Note. References 106 and 107 are on p. 51
The rearrangement was carried out as a part of a kinetic study (ref. 9). The product was not isolated.
† This represents percent conversion (or percent yield) during a kinetic study at the temperature indicated (ref. 9).
‡ The product could not be isolated, but the yield was good.
§ The reaction was unsuccessful.
¶ The yield is based on imidate.
† The product is diphenylamine-4-carboxylic acid
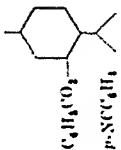‡ The product is N-benzoyl-4-carboxylic acid
§ The product is N-benzoyl-4-chloro)phenylamine-4-carboxylic acid.
¶ The rearrangement was

TABLE I—Continued

ARYL N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

| Aryl N-Arylbenzimidate $\begin{matrix}OR'\\ \| \\ R''-C-NR'\end{matrix}$ Substituents in R''—C—NR' | | | Yield, % (Ref.) | Conditions for Rearrangement (Ref.) | N-Aroyldiarylamine $\begin{matrix}R\\ \| \\ R''-C-N-R'\\ \|\| \\ O\end{matrix}$ Yield, % (Ref.) | Diarylamine (RNHR') Yield, % (Ref.) | References |
R	R'	R''					
[structure: cyclohexane with isopropyl and methyl] $C_6H_3(CO_2$	p-ClC$_6$H$_4$	C$_6$H$_5$	88	230–295°	—**	70††	15
p-NCC$_6$H$_4$	p-NCC$_6$H$_4$	C$_6$H$_5$	82	230–300°; 1.25 hr.	—	—	32
p-NCC$_6$H$_4$	2-O$_2$N-4-NCC$_6$H$_3$	C$_6$H$_5$	78	Boiling Dowtherm; 1–2 hr.	—††	85	29
p-NCC$_6$H$_4$	2-CH$_3$-4-NCC$_6$H$_3$	C$_6$H$_6$	45	207°; 1.5 hr.	—	—	29
o-CH$_3$COC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	—	207°; 1.5 hr. (3)	—‡‡	—	3
p-CH$_3$COC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	45 (?)	242°; 1.5 hr. (3)	92*†	—§§	3, 9
o-CH$_3$O$_2$(CC)H$_4$	C$_6$H$_5$	C$_6$H$_5$	74	208°; 45 min.	20	89	35
p-C$_6$H$_5$COC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	82	270–280°; 40 min.	90		31
2,4-Cl$_2$C$_6$H$_3$	C$_6$H$_5$	C$_6$H$_5$		242°; 1.5 hr.	93‡		3
2,4-Cl$_2$C$_6$H$_3$	p-ClC$_6$H$_4$	p-CH$_3$C$_6$H$_4$		280–300°; 2.5 hr.	—		15
2,4-Cl$_2$C$_6$H$_3$	o-CH$_3$C$_6$H$_4$	C$_6$H$_5$		—	—	~80	10
2,4-Cl$_2$C$_6$H$_3$	2,4-Cl$_2$C$_6$H$_3$	C$_6$H$_5$		290–300°; 2 hr.	—		10
3,5-Cl$_2$C$_6$H$_3$	3,5-Cl$_2$C$_6$H$_3$	C$_6$H$_5$		—	—		4
4-Cl-2-BrC$_6$H$_3$	o-BrC$_6$H$_4$	C$_6$H$_5$	71	230–240°; 2.5 hr.	42–55	71–70	17
2-Cl-4-NCC$_6$H$_3$	p-NCC$_6$H$_4$	C$_6$H$_5$	25	Boiling Dowtherm; 1–2 hr.	84	60	100, 29
2-Cl-4-NCC$_6$H$_3$	2-CH$_3$-4-NCC$_6$H$_3$	C$_6$H$_5$	38	Boiling Dowtherm; 1–2 hr.	80	73	29
(2-Br-1-C$_6$H$_3$)NC$_6$H$_3$	2-BrC$_6$H$_4$	C$_6$H$_5$	74	240–255°; 2.5 hr.	98–90	78	100
2-O$_2$N-4-NCC$_6$H$_3$	p-NCC$_6$H$_4$	C$_6$H$_5$	90	Boiling anisole or pyridine	90	—	29
2-O$_2$N-4-NCC$_6$H$_3$	2-O$_2$N-4-NCC$_6$H$_3$	C$_6$H$_5$	90	Boiling Dowtherm; 1–2 hr.	88	80	29
2-CH$_3$O-4-NCC$_6$H$_3$	p-NCC$_6$H$_4$	C$_6$H$_5$					29

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2-CH₃-4-NCC₆H₄	C₆H₄	Boiling Dowtherm: 1-2 hr.	70	94	85	29
2-CH₃-4-NCC₆H₄	C₆H₄	1-2 hr.	83	98	33	29
2,4,6-C₆H₄	C₆H₄	220-270° (3)			—(6)	3, 4
2,4,6-C₆H₄	C₆H₄	250-270°; 2 hr.			~40	4
2,4,6-C₆H₄	C₆H₄	250-270°; 2 hr.	80	>11	~80	4
2,4,6-C₆H₄	C₆H₄	250-270°; 2 hr.	88	98	92	6
2,4-CH₃OC₆H₄	C₆H₄	250-270°; 2 hr.	65	81		15
2,4,6-C₆H₄	C₆H₄	260-300°	65			23
2,4,4'(NO₂)₃C₆H₄	C₆H₄		24	***		1
2,6-(+4 CH₃)C₆H₄	C₆H₄	Boiling Dowtherm; 1-2 hr.	75	54		29
4,6-(2-CH₃)C₆H₃	C₆H₅	Boiling C₆H₅OC₆H₅; 10 min.	90	56		23
2,6-(+OCH₃)C₆H₄	C₆H₅		91			23
2,6-(+CH₃O₂C)C₆H₄	C₆H₅	Boiling o-C₆H₄Cl₂; 80 min	71	95		23
2,6-(4-o-C₆H₄O)C₆H₃	C₆H₅		92	**		23
2-(br-4-CH₃O₂C)C₆H₃-4-CH₃O₂CC₆H₄	C₆H₅	260°, 1.5 hr.	91	**		34
8-Quinolinyl	C₆H₅	260°, 1.5 hr.	74	80†		3
4-Quinolinyl	C₆H₅	280°, 20 min.	71	82†		3
8-Quinolinyl	-OCH₃C₆H₄	250°, 10 min.	47	72		30
8-Quinolinyl	C₆H₅		62	**		30
8-Quinolinyl	C₆H₅		59			30
2-Br-4,6-(CH₃)₂C₆H₂	C₆H₅		56	***		30
5,7-Cl₂-8-quinolinyl	C₆H₅	200°, few min.	21			30

Note: References 108 and 107 are on p. 51.

* The rearrangement was carried out as part of a kinetic study (ref. 9). The product was not isolated.

† The percent conversion (not the percent yield) was indicated; during a kinetic study the rearrangement was carried out at 260-310° but the yield was not...

‡ The reaction was unsuccessful.

§ The product underwent decomposition at once to 1-menthene, benzoic acid, and 8-Chloroacridine.
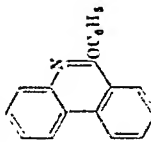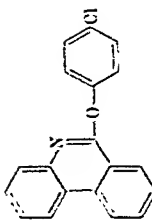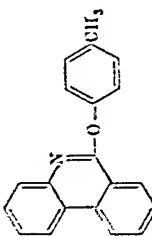
|| The product was obtained by pyrolysis of 4,4'-diamino-N-benzoyldiphenylamine.

¶ 1-Phenyl-2-quinolone was obtained

** N'-Phenylanilide was obtained

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TABLE I—*Continued*

ARYL N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

Substituents in R''—C...NR'			Aryl N-Arylbenzimidate R''—C(OH)...NR' Yield, % (Ref.)	Conditions for Rearrangement (Ref.)	N-Aroyldiarylamine R''-C(=O)-N(R)(R') Yield, % (Ref.)	Diarylamine RNHR' Yield, % (Ref.)	References
R	R'	R''					
			91	350°; 2 hr.	60		20
			93	350°; 2 hr.	75		20
			91	300°; 2 hr.	70		20

Note: References 106 and 107 are on p. 51.

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TABLE II

DIARYLAMINE-2-CARBOXYLIC ACIDS

		Aryl N-Arylbenzimidate Substituents [b]	N-Aroyldiarylamine		2-Carboxylic Acid		Diarylamine-2-carboxylic Acid					
			2-Carboxylic Ester		2-Carboxylic Acid							
R	R'	Yield, % (Ref.)	Yield, % (Ref.)	Conditions Rearrangement	Yield, % (Ref.)	Yield, % (Ref.)	Yield, % (Ref.)[a]	Substituents	Method (Ref.)	Yield, %	Acridone	Refs.
H	C_6H_5	62 (36, 81 (15)	73 (15)	270–5°, 10 min. (15)	85–91	75 (15)	79 (36) 96 (15)	—	b[f] (15)	?		15, 36
H	o-$CH_3C_6H_4$	88		270–300°, few minutes		78	Almost quant.	2-Cl	a	80		107
H	p-ClC_6H_4											15
H	o-CH_3,p-ClC_6H_4, 70	83	280–235°, 12 min		—	25–40‡		b	87		44
H	o-$C_6H_4O_2CCH_3C_6H_4$ 83	91	260–265°, 13 min		—	—					44
H	$2,4$-$C_6H_4Cl_2$	72	65	260–265°, 10 min		74	63					15
H	$2,4$-$(CH_3)_2C_6H_3$	56	89	275° 10 min		—	28‡	2,4-$(CH_3)_2$	d‡	71		15
3-Cl	p-ClC_6H_4			210–215°, 70 min		—	—	1-Cl-7-OCH$_3$‡	c		—	46

Note: References 106 and 107 are on p. 51.
[a] The yield is based on the N-benzoyl ester.
[b] Pyrolysis of N-benzoyl ester.
[c] Pyrolysis of N-acetyl ester.
[d] Treatment of diarylamine 2nitrile, with POCl$_3$, followed by hydrolysis.
* The yield is based on the N-benzoyl ester.
† 2-Carbox(phenylamine-2-acetic acid was obtained.
‡ The yield is based on methyl 6-chlorosalicylate
§ The 9-chloroacridine was synthesized
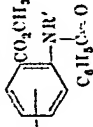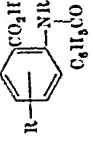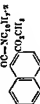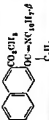
49

TABLE II—Continued

DIARYLAMINE-2-CARBOXYLIC ACIDS

| Aryl N-Arylbenzimidate (substituents in) | | | | N-Aroyldiarylamino | | Diarylamine-2-carboxylic Acid | | | | Acetone | |
R	R'	Yield, % (Ref.)	Conditions for Rearrangement	2-Carboxylic Ester Yield, % (Ref.)	2-Carboxylic Acid Yield, % (Ref.)	Yield, %* (Ref.)	Substituent	Method (Ref.)	Yield, %	Refs.
4-Cl	p-CH$_3$OC$_6$H$_4$	—	200–210°; 10 min.	—	—	—	2-Cl-7-OCH$_3$	b	Almost quant.	15
5-OCH$_3$	o-ClC$_6$H$_4$	80	270°; 10 min.	—	—	—	5-Cl-3-OCH$_3$	a, b	—	40
5-OCH$_3$	m-ClC$_6$H$_4$	83	270–310°	80	—	—	1-Cl-6-OCH$_3$**	c	—	41
5-OCH$_3$	p-ClC$_6$H$_4$	83	275–290°	92	—	77	2-Cl-6-OCH$_3$	a, b, c	—	42
5-OCH$_3$	p-IC$_6$H$_4$	50	290°	81	—	—	2-I-6-OCH$_3$	a, c	—	43
6-CH$_3$	C$_6$H$_5$	—	275°	81	—	—				37
6-CH$_3$	o-FC$_6$H$_4$	61 (30)	260–270° (37)	88 (37)	92 (30)					34
6-CH$_3$	o-ClC$_6$H$_4$	72 (30) / 75 (37)	280°	80		— (30)	4-Cl-5-CH$_3$	b (30)	80	36, 37
6-CH$_3$	o-BrC$_6$H$_4$	—	290°	70	08					34
6-CH$_3$	o-CH$_3$C$_6$H$_4$	60	270°	70						37
6-CH$_3$	p-CH$_3$C$_6$H$_4$	—	285–290°	83						38
6-CH$_3$	2,4-(CH$_3$)$_2$C$_6$H$_3$	60	275°	82						34
6-CH$_3$	2-Cl-4-BrC$_6$H$_3$	—	285°	70						34
6-CH$_3$	2-Cl-4-CH$_3$OC$_6$H$_3$	—	286–290°	†						34
6-CH$_3$	2-Cl-4-CH$_3$C$_6$H$_4$	—		††						34
6-CH$_3$	2,4,6-(CH$_3$)$_3$C$_6$H$_2$	—	270–300°; 15 min.	††						34
6-CH$_3$	α-C$_{10}$H$_7$	70					5-CH$_3$-3,4-benzo	a	72	48
6-CH$_3$	β-C$_{10}$H$_7$	63	300°; 0.5 hr.	††			5-CH$_3$-1,2-benzo	a	38	48

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										37	47
										34	47
						$2,4,5,7$-Cl_4	d		10		
						$2,4,7$-Br_3	b		54 (105)	81	15,105
							c		91 (16)		
							d		87 (105)		
				90 (15)	86–94 (105)	$2,4,5,7$-Br_4			66	105	
					5 min.						
						$1,2,7,8$-Dibenzo	a		80	49	
						$3,4,5,6$-Dibenzo	a		47	48	
						$1,2,6,7$-Dibenzo	a		54	48	

$4,6$-Cl_2			84	220°			
$4,6$-Cl_2	C_6H_5		85	280°, 10 min.			
$2,4$-(CH_3)$_2C_6H_3$‡‡							
$4,6$-Br_2	C_6H_5		86	100–200°	80		
$4,6$-Br_2	p-BrC$_6$H$_4$		65 (15)	270° (15)	87 (15)		
					(105)		
				200–210°	86–94 (105)		
				(105)			
			—	200°,	80		
$2,4$-Br$_2$C$_6$H$_3$				5 min.			

CO_2H
| O=C—NC$_{10}$H$_7$-β | | — | †† | 280–300°, 15 min. | | |
| C_6H_5 | | | | | | |

| | CO_2CH_3 | 74 | | 280–500°, 0.5 hr. | †† | |
| | C_6H_5 | | | | | |

CO_2H
| O=C—NC$_{10}$H$_7$-β | | 51 | †† | 350–500° | †† | |
| C_6H_5 | | | | | | |

Note. References 106 and 107 below.

* The yield is based on the N-benzoyl ester.
† The reaction was unsuccessful.
†† Both the acridone and the ethyl esters were used.
‡ This is the probable structure of the product.
** Pyrolysis gave the acridone directly.
‡‡ The ethyl ester was used instead of the methyl ester.

^a Pyrolysis of N-benzoyl ester.
^b Pyrolysis of N-benzoyl acid.
^c Treatment of the ester with iodide acid.
^d Treatment of diarylamine, R₂NHₐᵣ, with POCl₃, followed by hydrolysis.

REFERENCES

¹⁰⁶ Gilman and Zuech, *J. Org. Chem.*, **26**, 2013 (1961).
¹⁰⁷ Buchanan and Graham, *J. Chem. Soc*, 1950, 500.

CHAPTER 2

α-AMIDOALKYLATIONS AT CARBON

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CONTENTS

INTRODUCTION

This chapter is concerned with reactions which lead to the formation of a new carbon-carbon bond by replacement of X from the electrophilic reagent $RCON(R')CH(R'')X$, where X is halogen, —OH, —OR, —OCOR, —NHCOR, —NR_2 or —$\overset{\oplus}{N}R_3$. The group R' may be hydrogen or alkyl or, in important instances, a second acyl group, as in the corresponding derivatives of phthalimide, $o\text{-}C_6H_4(CO)_2NCH(R'')X$. In a few cases a sulfonyl group may replace the acyl group of the electrophilic reagent.

The nucleophiles that react with these reagents fall into two broad groups: aromatic compounds and aliphatic compounds containing reactive methylene or methine groups. The first may be illustrated by the phthalimidomethylation of benzene, and the second by the reaction of ethyl acetoacetate with N,N'-benzylidenebisacetamide.

$$o\text{-}C_6H_4(CO)_2NCH_2OH \ + \ C_6H_6 \ \xrightarrow{H_2SO_4} \ o\text{-}C_6H_4(CO)_2NCH_2C_6H_5 \ + \ H_2O$$

$$C_6H_5CH(NHCOCH_3)_2 \ + \ CH_3COCH_2CO_2C_2H_5 \ \xrightarrow{(CH_3CO)_2O}$$
$$C_6H_5CH(NHCOCH_3)CH(COCH_3)CO_2C_2H_5 \ + \ CH_3CONH_2$$
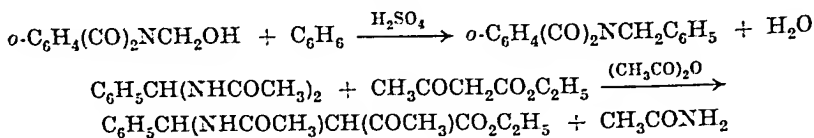
Also included in this review are the methods for preparing the electrophilic reagents. They are followed by a listing of compounds structurally related to them, and which, consequently, must be regarded as potential amidoalkylating agents. Portions of the material in this chapter have been reviewed elsewhere.[1,2]

MECHANISMS OF THE REACTIONS

The reactions considered in this chapter include acid-catalyzed, base-catalyzed, and thermally induced processes. They, like the corresponding α-aminoalkylation reactions,[3] probably encompass a considerable portion of the mechanistic spectrum of heterolytic organic chemistry. Detailed studies are almost completely lacking. Nevertheless, some general outlines of the mechanistic possibilities can be drawn.

Although cryoscopic studies in 100% sulfuric acid have yet to be reported, it seems likely that, in very strong acids of high dielectric constant, electrophiles lacking a hydrogen atom on the nitrogen atom undergo appreciable dissociation to a carbonium-immonium ion. In the

[1] Hellmann, *Angew. Chem.*, 69, 463 (1957).
[2] Schröter in *Houben-Weyl Methoden der Organischen Chemie*. Vol. XI/1, 4th ed., G. Thieme, Stuttgart, 1957, pp. 795-805.
[3] Hellmann and Opitz, *α-Aminoalkylierung*. Verlag Chemie, GMBH, Weinheim, 1960, pp. 64-79.

presence of weak nucleophiles (e.g., aromatic rings) bimolecular electro-

$$RCON(R')CH_2X \rightleftharpoons \begin{bmatrix} RCO(R')\overset{\oplus}{N}CH_2 \\ RCO(R')N=\overset{\oplus}{C}H_2 \end{bmatrix} + HX$$
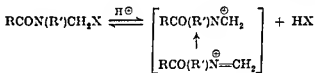
philic displacement (S_E2) of protons from C—H bonds usually follows. Under the same conditions amide derivatives having a hydrogen atom attached to the nitrogen atom (R' = H) may give the analogous cation, but other forms are more likely. Thus, when nitriles are treated with formaldehyde in strong sulfuric acid, sulfur-containing intermediates have been isolated.[4,5] Evidence indicates that these are sulfate esters which in strong acid equilibrate with their corresponding carbonium ions.[4–6] Granting the existence of these structures, identical species should, of course, be formed when the amide, RCONHCH$_2$X, is dissolved in strong

$$RCN + CH_2O \xrightarrow{H_2SO_4} RC=NCH_2X \underset{OSO_3H}{\overset{H^{\oplus}}{\rightleftharpoons}} RC=\overset{\oplus}{N}CH_2 + HX$$
$$\underset{OSO_3H}{} \quad \underset{OSO_3H}{}$$
$$(X = OH \text{ or } N=C(R)OSO_3H)$$
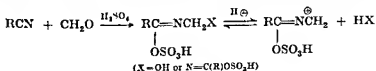
sulfuric acid. That such a common electrophilic intermediate is present is suggested by the recent finding that nitriles and formaldehyde in either strong sulfuric or strong phosphoric acid can substitute effectively for the corresponding methylolamides in the amidomethylation of aromatic compounds.[5]

In acid-catalyzed processes associated with media of low dielectric constant it is unlikely that appreciable preformed concentrations of carbonium ions are present. In such processes, reaction with weak nucleophiles probably involves either tight ion pairs or incipient carbonium ions formed by an S_N1 process.

Reactions in neutral or basic media of amide derivatives

$$RCON(R')CH(R')X$$
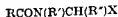
lacking a hydrogen atom on the nitrogen atom exhibit characteristics of S_N2 processes. Thus, more nucleophilic reactants are usually required under these conditions, and reactivity toward comparable nucleophiles generally diminishes with decreasing stability of the leaving group X, i.e., halide ion $\sim R_3N > OH > \overset{\ominus}{O}R$. It must be recognized, however,

[4] Magat, Faris, Reith, and Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951).
[5] Parris and Christenson, *J. Org. Chem.*, **25**, 1888 (1960).
[6] Mowry and Ringwald, *J. Am. Chem. Soc.*, **72**, 4439 (1950).

that even under these conditions the presence of proton donors can assist the removal of X by an acid-catalyzed process. These considerations also apply to similar reactions of amide derivatives with $R' = H$, but with the added opportunity for a mechanism involving an azomethine intermediate. This elimination-addition scheme appears to provide the most attractive mechanism for most of the thermally induced amido-alkylation reactions.

$$RCONHCH(R')X \xrightarrow{-HX} RCON{=}CHR' \xrightarrow{HA} RCONHCH(R')A$$
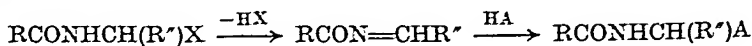
SCOPE AND LIMITATIONS

General Considerations

The N-methylol-amides and -imides are the most important electrophiles to be dealt with here. They are readily prepared by the reaction of formaldehyde with primary amides and imides, and their stability toward heat and acid is sufficient to permit their use under drastic reaction conditions. Furthermore, they can be employed as intermediates for the preparation of most of the other useful electrophiles.

$$RCONHCH_2OH \longrightarrow
\begin{cases}
\xrightarrow{HX} & RCONHCH_2X \\
\xrightarrow{ROH,H^{\ominus}} & RCONHCH_2OR \\
\xrightarrow{R_2NH} & RCONHCH_2NR_2 \\
\xrightarrow{RCONH_2} & (RCONH)_2CH_2
\end{cases}$$
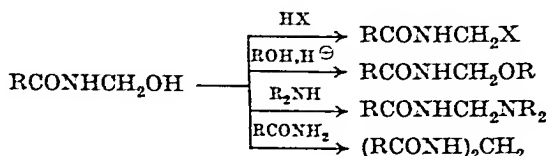
Unlike formaldehyde, most higher aldehydes in their reactions with amides do not stop at the $RCHOHNHCOR'$ stage but react further to produce N,N'-alkylidenebisamides, $RCH(NHCOR')_2$. Thus, whereas the amidomethylation reaction permits a relatively broad selection of electrophilic reagents, the homologous α-amidoalkylation reactions have been restricted almost exclusively to the use of N,N'-alkylidene- and N,N'-arylidene-bisamides. As the reactivities of these derivatives often are to be found at the lower end of the electrophilic scale, their usefulness is further limited by the consequent requirement of comparatively high nucleophilic reactivity for the other reactant.

Structural Considerations

Structure of the Electrophile. Any structural feature tending to stabilize an incipient carbonium ion in either an S_N1 or an S_N2 process must enhance the rate of reaction with a given nucleophile. However, if ionization is not rate-limiting, the reverse is true, since stabilization of

a *preformed* cation must thereby decrease its tendency to lose its charge through electrophilic attack. Therefore, in going from reaction conditions where an S_N1 or S_N2 mechanism prevails to a situation favoring the rapid pre-equilibrium production of carbonium ions (solvated or paired), one would expect to encounter an inversion in the reactivity sequence of a series of electrophiles. No quantitative work has been reported for α-amidoalkylation reagents. Nevertheless, indication that such an inversion in sequence applies to these reagents follows from a qualitative consideration of the results of several workers.

de Diesbach studied the reactions of a series of N-methylolamides in concentrated sulfuric acid at room temperature.[7] He found that amidomethylation of 1,3-dimethylanthraquinone in the 4-position succeeded with N-methyloltrichloroacetamide and N-methylolphthalimide but failed with N-methylolbenzamide. Phenanthrenequinone gave both a 2-mono- and a 2,7-di-substituted product with N-methyloltrichloroacetamide and N-methylolphthalimide, but only the monosubstitution product with N-methylolchloroacetamide. 2,4-Dimethylbenzophenone gave both a 5-mono- and a 3,5-di-substituted product with N-methylolphthalimide, but only the monosubstitution product with N-methyloltrichloroacetamide. These results enable one to construct the qualitative reactivity sequence: $o\text{-}C_6H_4(CO)_2NCH_2OH > CCl_3CONHCH_2OH > CH_2ClCONHCH_2OH > C_6H_5CONHCH_2OH$. This order is the reverse of that expected for the stabilities of the corresponding carbonium ions (i.e., delocalization of the type $RCONHCH_2 \leftrightarrow RCONH=CH_2$ should be greatest for the benzamide derivative) and suggests that, in *concentrated sulfuric acid*, reactivity is determined by the relative electrophilicities of preformed carbonium ions.

Tawney and co-workers prepared N-methylol- and N-chloromethylmaleimide and compared their chemical properties with those of the corresponding phthalimide derivatives.[8] Although direct comparisons of their reactivities with aromatic compounds were not made, these investigators did establish that the hydroxyl group of N-methylolmaleimide was readily displaced by amines in dioxane solution and by o-nitrotoluene in concentrated sulfuric acid, and that N-chloromethylmaleimide readily underwent the zinc chloride-catalyzed reaction with benzene and phenol. However, unlike the corresponding phthalimide derivatives, N-methylolmaleimide would not react with hydrochloric acid to give the N-chloromethyl derivative, nor would the latter solvolyze in ethanol to give N-ethoxymethylmaleimide. Tawney and co-workers explained these striking differences by suggesting that the nitrogen atom in the maleimide,

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[7] de Diesbach, *Helv. Chim. Acta*, **23**, 1232 (1940).

[8] Tawney, Snyder, Conger, Leibbrand, Stiteler, and Williams, *J. Org Chem.*, **26**, 15 (1961).

being more electronegative than that in the phthalimide, renders stabilization of the *incipient* carbonium ion

$$(CO)_2 \overset{\curvearrowright}{N} - \overset{\delta+}{CH_2} \cdots \overset{\delta-}{X}$$
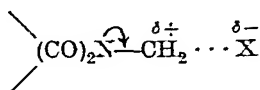
less effective in the former derivative. In an $S_N 1$ process this would retard rate-limiting ionization, and in an $S_N 2$ process it would make bond forming more important in the transition state and require a greater nucleophilicity of the attacking reagent.

The ultimate effect of this trend can be approached by substituting other electronegative groups directly on the methylol carbon atom. Esters of 5-hydroxy-5-hydantoincarboxylic acid gave only the corresponding amides with primary amines.[9] The hydroxyl group remained unaffected. Apparently, so many electronegative groups are attached
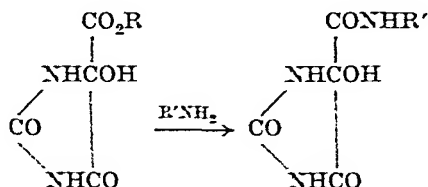
to the usually reactive methylol carbon atom that insufficient development of positive charge in the transition state is available even for the attack of strongly nucleophilic amines. One might predict, however, that, if a carbonium ion could be generated from this or related hydroxyhydantoins, electrophilic reagents more reactive than anything obtainable from the simple methylolamides would be produced.

Clearly, in an electrophilic reagent that reacts by a pre-equilibrium dissociation the nature of the anionic leaving group is immaterial. The most easily accessible derivative then becomes the reagent of choice. In view of the ready availability of N-methylolamides, it is not surprising that they have been used to the virtual exclusion of other α-amidoalkyl derivatives *when strong sulfuric acid is the reaction medium.* It is only under less drastic reaction conditions, or when a more active nucleophile is involved, that the stability of the group departing from the electrophile becomes significant. This will become more apparent from a consideration of the effect of nucleophile structure on the scope of these reactions.

Structure of the Nucleophile. As already indicated, two general groups of nucleophiles fall within the scope of this chapter: aromatic

compounds and aliphatic compounds containing an active hydrogen atom attached to a carbon atom. The range of aromatic reactivity can best be illustrated by consideration of four examples: benzoic acid, benzene, phenol, and 2-naphthol.

As expected of such a poor nucleophile, benzoic acid requires reaction conditions ensuring attack by a strongly electrophilic species. Thus all the successful amidomethylations of benzoic acid so far reported involve reaction of a methylolamide in concentrated sulfuric acid at room temperature. Although N-methylolbenzamide gives the 3-amidomethylated product in only 8% yield *under these conditions*,[10] N-methylolchloroacetamide[11] and N-methylolphthalimide[12] are converted in 54% and 60% yields, respectively. Again, these results agree with expectations based

$$C_6H_5CO_2H + RCON(R')CH_2OH \xrightarrow[H_2SO_4]{Concd.} \text{\raisebox{0pt}{$\underset{CH_2N(R')COR}{\overset{CO_2H}{\bigotimes}}$}}$$
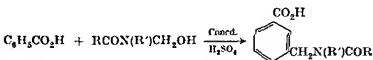
on previous considerations of relative electrophilic reactivities in strong sulfuric acid.

Benzene is readily substituted under similar conditions. Indeed, a 32% yield of a 1,4-disubstituted product has been reported with N-methylolbenzamide in concentrated sulfuric acid.[13] Such drastic conditions, however, are not required for simple substitution. Although N-bromomethylphthalimide is inert in boiling benzene, addition of a trace of anhydrous zinc chloride suffices to catalyze an exothermic reaction leading to N-benzylphthalimide in 94% yield.[14]

$$o\text{-}C_6H_4(CO)_2NCH_2Br \xrightarrow[ZnCl_2]{C_6H_6} o\text{-}C_6H_4(CO)_2NCH_2C_6H_5$$
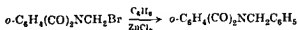
Phenol, which does not react with N-methylolphthalimide in boiling benzene, is readily attacked by N-bromomethylphthalimide under similar conditions even in the absence of a Lewis acid catalyst. A 51% yield of a mixture of approximately equal amounts of 2- and 4-phthalimidomethylphenol is obtained.[14] Interestingly, no 2,4-diphthalimidomethylphenol

[10] Einhorn, Bischhoff, and Szelinski, *Ann.*, **343**, 223 (1905)

[11] Einhorn and Mauermayer, *Ann.*, **343**, 282 (1905).

[12] Oda, Teramura, Tanimoto, Nomura, Suda, and Matsuda, *Bull. Inst. Chem. Res. Kyoto Univ.*, **33**, 117 (1955) [C.A., **51**, 11255 (1957)].

[13] Nenitzescu and Dinulescu, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **2**, 47 (1954). *Commun. Acad. Rep. Populare Romîne*, **4**, 45 (1954) [C A., **50**, 15445 (1956)].

[14] H. E. Zaugg, unpublished data

[15] Zaugg and Schaefer, *J. Org. Chem.* **28**, 2925 (1963)

is formed.   This material accounts for 32% of the product when phenol is treated with N-methylolphthalimide in concentrated sulfuric acid.[15,16]

2-Naphthol represents a near approach to the ultimate in nucleophilic reactivity toward α-amidoalkylation reagents.   At room temperature in an ethanol solution containing 1–2% of hydrochloric acid, it reacts with N-methylolbenzamide to give 1-benzamidomethyl-2-naphthol quantitatively in 2 hours.[10]   (The more nucleophilic aromatic heterocycles, such as the polymethylpyrroles,[17] also resemble 2-naphthol in their reactivity toward various methylolamides.)   2-Naphthol is sufficiently nucleophilic to undergo smooth α-amidoalkylation with N,N'-methylene- and N,N'-arylidene-bisamides.[18]   Although phenols and even phenol ethers and

$$\text{(naphthol-OH)} + (CH_3CONH)_2CH_2 \xrightarrow[65°]{POCl_3, CHCl_3}$$

$$\text{(CH}_2\text{NHCOCH}_3\text{-naphthol-OH)} \quad (94\%) \quad + \quad CH_3CONH_2$$
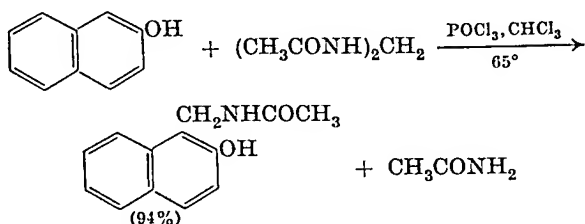
esters react in like manner, the diminished reactivity of the bisamides clearly restricts their usefulness in the aromatic series to substitution in activated rings.

Conceivably, aromatic nucleophilicity could be increased by employing an aromatic Grignard reagent.   The orientational ambiguity often associated with the direct substitution methods also would be obviated thereby.   The only example of this approach however, appears to be the reaction of phenylmagnesium bromide with N-benzoyldiphenylketimine (see p. 77).[19]

Aliphatic compounds containing methyl, methylene, or methine groups sufficiently reactive to undergo α-amidoalkylation represent a wide variety of structural types.   They include cyclic and acyclic β-dicarbonyl compounds of all types, β-cyano esters, activated nitriles, nitro alkanes and β-nitro esters, certain non-aromatic heterocyclic compounds with active methine groups in the ring, heteroaromatic compounds with activated methyl groups, acetylene, and hydrocyanic acid.   Most of these types possess nucleophilic reactivity in the range of that possessed by phenol in the aromatic series.   Hence some of them can undergo reaction with the whole range of α-amidoalkylation reagents, including the weakly

[16] Tschcrninc, Ger. pat. 134, 979 (*Chem. Zentr.*, 1902, II, 1084).

[17] Fischer and Nenitzescu, *Ann.*, 443, 113 (1925).

[18] Inhidate, Sekiya, and Yannihara, *Chem. Ber.*, 93, 2898 (1960).

[19] Ivanoff, *Doklady Akad. Nauk SSSR*, 109, 537 (1956) [*C.A.*, 51, 4997 (1957)].

electrophilic N,N'-bisamides. However, unlike the aromatic nucleophiles, many of the reactive methylene compounds are unstable or undergo side reactions in strong acid. For this reason and because their corresponding anions invariably exhibit enhanced nucleophilic reactivities, α-amidoalkylations of these weak aliphatic acids are usually conducted in neutral or basic media.

α-Amidoalkylation of Aromatic Carbon Atoms

With N-Methylol-amides and -imides (the Tscherniac-Einhorn Reaction). In 1902 Tscherniac reported the condensation of N-methylolphthalimide with a series of aromatic compounds in concentrated or fuming sulfuric acid.[15] Subsequently Einhorn extended the reaction to a variety of readily available N-methylolamides.[10,11,20–26] The Tscherniac-Einhorn reaction,[1,2] together with its more recently developed variations (see below), bears a superficial relationship to the well-known Mannich

$$RCONHCH_2OH + ArH \xrightarrow{H_2SO_4} RCONHCH_2Ar$$

reaction.[3,27] However, the latter is usually restricted to the preparation of tertiary benzylamines, whereas amidomethylation, through hydrolysis of initial products, provides a route to primary benzylamines. Furthermore, the scope of the Mannich reaction in the aromatic series is generally restricted to phenols or to equally nucleophilic ring systems. In contrast, some of the reagents available for amidomethylation are even more electrophilic than the usual acylation reagents of the Friedel-Crafts reaction. Consequently the scope of some of the amidomethylations can be extended to aromatic systems usually considered rather inert to substitution.

The facile amidomethylation of benzoic acid has already been discussed. Although experimental details have been reported only for chlorobenzene,[13] successful amidomethylation of the other halobenzenes and of benzonitrile and benzenesulfonamide has been claimed.[28] Benzophenone reportedly is inert to N-methylolamides in concentrated sulfuric acid, but

[20] Einhorn, Ger. pat. 156,398 (*Chem. Zentr.*, 1905, I, 55)
[21] Einhorn and Göttler, *Ber.*, 42, 4837 (1909)
[22] Einhorn and Ladisch, *Ann.*, 343, 264 (1905)
[23] Einhorn and Ladisch, *Ann.*, 343, 265 (1905)
[24] Einhorn and Ladisch, *Ann.*, 343, 277 (1905)
[25] Einhorn and Schupp, *Ann.*, 343, 252 (1905)
[26] Einhorn and Sprongerts, *Ann.*, 361, 161 (1908)
[27] Blicke, in Adams, *Organic Reactions*, Vol. I, John Wiley & Sons, New York, 1942, p. 303.
[28] O'Cinnéide, *Nature*, 175, 47 (1955).

its methyl and hydroxyl derivatives are easily substituted.[7] Even nitro-benzene is subject to attack. In his original patent Tscherniac stated that a 3-substituted nitrobenzene could be obtained from N-methylol-phthalimide either in concentrated sulfuric acid at 50° or in fuming sulfuric acid at room temperature.[16] More recently the isolation of 3,5-bisphthal-imidomethylnitrobenzene has been reported using 20% oleum as the condensing agent.[29]

Because of its clear superiority over other readily available reagents, N-methylolphthalimide has been used most frequently in the Tscherniac-Einhorn reaction. This superiority arises from the high order of stability and reactivity of N-methylolphthalimide in strong sulfuric acid and from its ability to form crystalline readily isolable products from which, if desired, the phthalimido group can be removed easily.[30] Notwith-standing the fact that benzamides are generally more difficult to hydrolyze than trichloroacetamides or even chloroacetamides, N-methylolbenzamide is used as frequently as the methylol derivatives of the two preceding halogenated amides. Examples of the use of N-methylol derivatives of most of the commonly available amides or imides are to be found. Yet, aside from their requirement for the synthesis of specifically desired derivatives, none appears to provide any particular advantage over the generally preferred reagents. The hitherto unreported N-methyloltri-fluoroacetamide, $CF_3CONHCH_2OH$ (see p. 130), however, might show some superiority over the common reagents. In strong sulfuric acid it should be even more reactive than its trichloro analog, and the extra-ordinary ease of alkaline hydrolysis of trifluoroacetamide derivatives[31] would make it a convenient reagent for the preparation of benzylamines.

Because they are more difficult to isolate, N-methylol derivatives of monosubstituted amides, i.e., $RCON(R')CH_2OH$, are seldom used.[32,33] However, Buc has avoided this difficulty in the case of the two lactams, 2-pyrrolidinone and γ-valerolactam, merely by using a mixture of the amide and paraformaldehyde in concentrated sulfuric acid.[34]

N,N'-Dimethylol derivatives of dicarboxamides and of urea have also been employed. For example, 1,3-dimethylolurea (1) and ethyl 2-furoate condense in concentrated sulfuric acid to give the symmet-rically disubstituted urea 2 in 93% yield.[35] N,N'-Dimethyloloxamide,

[29] Buc, U.S. pat. 2,593,840 [C.A., 46, 6844 (1952)].
[30] Ing and Manske, J. Chem. Soc., 1926, 2348; Sheehan and Frank, J. Am. Chem. Soc., 71, 1856 (1949).
[31] Weygand and Reiher, Chem. Ber., 88, 26 (1955), and previous references.
[32] Böhme, Dick, and Driesen, Chem. Ber., 94, 1879 (1961).
[33] Böhme, Driesen, and Schünemann, Arch. Pharm., 294, 344 (1961).
[34] Buc, U.S. pat. 2,652,403 [C.A., 48, 11495 (1954)].
[35] Moldenhauer, Irion, and Marwitz, Ann., 583, 37 (1953).

(CONHCH₂OH)₂, reacts similarly.[35] Several reactions of 1,3-dimethylol-

$$CO(NHCH_2OH)_2 + \text{（furan CO}_2C_2H_5\text{）} \xrightarrow{H_2SO_4} CO\left[NHCH_2\text{（furan CO}_2C_2H_5\text{）}\right]_2$$

1 2
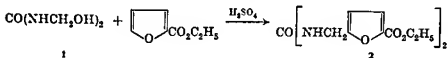
urea have been reported in which only one of the reactive centers is attacked.[36-40] Thus, with 4-nitrophenol in sulfuric acid diluted with glacial acetic acid, the unsymmetrical urea 3 is obtained.[40] Although a

3 4 5
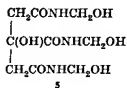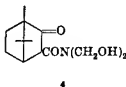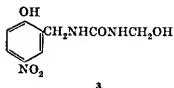
few N,N-dimethylolamides of type 4 are known,[41,42] as is N,N′,N″-trimethyloltricitramide (5),[43] Tscherniac-Einhorn reactions with such polyfunctional derivatives have not been reported.

A large majority of aromatic amidomethylations reported to date have been conducted either in concentrated sulfuric acid according to Tscherniac's original specifications or in the ethanolic hydrogen chloride medium used by Einhorn for substitution of the more nucleophilic aromatic systems. Despite its long history, remarkably few attempts to vary the conditions of the Tscherniac-Einhorn reaction have been reported. Even fewer qualify as reasonably systematic studies of reaction conditions. A careful investigation of the phthalimidomethylation of acetanilide has been reported by Ota, Kaneyuki, and Matsui.[44] They studied the effect of varying the sulfuric acid concentration on the reaction of equivalent quantities of acetanilide (1.6 g.) and N-methylolphthalimide (2.0 g.) at room temperature for 24 hours. In 99.5% sulfuric acid (8 ml.) only the *ortho* 6 and *para* 7 monosubstitution products were formed in 27 and 60% yields, respectively. However, in 4% oleum the yield of 7 decreased to

[35] de Diesbach, Swiss pat. 127,926–127,930 (*Chem. Zentr.*, 1929, I, 2243).
[36] de Diesbach, Ger. pat. 507,049 (*Chem. Zentr.*, 1932, II, 295).
[37] de Diesbach, Ger. pat. 511,210 (*Chem. Zentr.*, 1931, II, 2514).
[38] de Diesbach, Gubser, and Spoorenberg, *Helv. Chim. Acta*, 13, 1265 (1930).
[39] de Diesbach, Wanger, and Stockalper, *Helv. Chim. Acta*, 14, 355 (1931).
[40] Einhorn, *Ann.*, 361, 113 (1908).
[41] Einhorn, Ger. pat. 208,255 (*Chem. Zentr.*, 1909, I, 1281)
[42] Einhorn and Feibelmann, *Ann.*, 361, 140 (1908)
[43] Ota, Kaneyuki, and Matsui, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 81, 1849 (1960) [*C.A.*, 56, 2373 (1962)].

6% and the disubstituted product **8** was isolated in 66% yield. Only a trace of **6** was obtained.
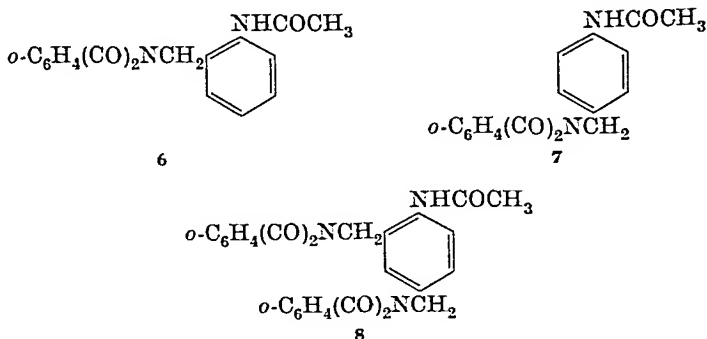
Similar results were observed with 4-methylacetanilide, but the activating effect of the methyl group in this substrate reduced the optimum sulfuric acid concentration to 97.7%. Under these conditions a mixture of the two possible monosubstitution products was formed in 78% yield. In 99.5% sulfuric acid only a 20% yield was obtained. That sulfonation as well as disubstitution played an important role in these experiments was demonstrated by the fact that, with acetanilide in 100% sulfuric acid, sulfonation occurred to the extent of 98% after 24 hours at room temperature, whereas, in 95% acid under the same conditions, sulfonation proceeded to the extent of 18%.

To minimize this undesirable property of sulfuric acid, other workers have used glacial acetic acid as a diluent.[13,40,45,46] In another instance the condensation of N-methylolchloroacetamide with phenylacetic acid was allowed to proceed in anhydrous hydrogen fluoride.[47] Other means of avoiding the use of sulfuric acid in this reaction have failed, however. They include p-toluenesulfonic acid in benzene and anhydrous zinc chloride in phosphorus oxychloride.

Several other media, however, have been employed successfully in condensations of N-methylolamides. Unfortunately, the aromatic substrates employed generally possessed reactive ring systems. Thus it is not possible to deduce whether any of these media could be substituted for strong sulfuric acid (or anhydrous hydrogen fluoride) under all possible conditions. The most likely candidates appear to be polyphosphoric acid, anhydrous aluminum chloride, or boron trifluoride. Polyphosphoric acid and 100% phosphoric acid alone or in glacial acetic

[44] de Diesbach, Swiss pat. 136,046 (*Chem. Zentr.*, 1930, I, 3355).

[46] de Diesbach, Swiss pat. 139,642–139,645 (*Chem. Zentr.*, 1931, I, 2120).

[47] Zaugg and Horrom, *J. Am. Chem. Soc.*, 80, 4317 (1958).

acid have brought about a few relatively easy amidomethylations,[48] and 85% phosphoric acid at 70–80° has effected the condensation of N-methylolacetamide with thiophene to give the amide 9 in yields of 50–60%.[49] Phosphorus pentoxide and phosphoric acid also have been used in the substitution of phthalocyanine dyes with N-methylolphthalimide.[50]

9

Aluminum chloride in dry acetone or glacial acetic acid has been found to catalyze the reaction of a number of N-methylolamides with several phenols and phenol ethers in yields ranging from 60 to 73%.[51] Although less reactive aromatic compounds were not included in this study, it was noted that the aluminum chloride-catalyzed reactions seemed to proceed faster than comparable ones in sulfuric acid. With boron trifluoride in benzene at 60°, N-methylol-N-methylacetamide gave the expected product, $CH_2CON(CH_3)CH_2C_6H_5$, in 68% yield.[32]

Several sets of mild conditions have been used for carrying out aromatic alkylations with N-methylolamides, but it is doubtful whether they possess any general advantages over the ethanolic hydrogen chloride method of Einhorn. A number of di- and tri-methoxybenzene derivatives[52] and some phenolic dyes[53] have been successfully condensed with N-methylolamides by using anhydrous zinc chloride in acetic acid, but no yields were reported. Anhydrous formic acid at 50° sufficed to condense 2,4-xylenol with several N-methylolurea derivatives;[54,55] and merely heating the two N-methylolfuranamides 10 ($n = 0$ and 1) above their melting points generated the polymers 11 ($n = 0$ and 1).[35] However, heating in the absence of acid cannot be relied on to effect amidomethylation even of
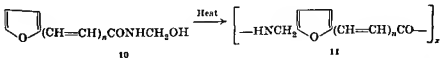
10   11

[48] Arzneimittelfabrik Krewel-Leuffen, Austrian pat 196,391 (1958) (Chem. Zentr., 1960, 16521).

[49] Hartough, Thiophene and Its Derivatives, Interscience Division, John Wiley & Sons, New York, 1952, p. 213.

[50] American Cyanamid Co , Brit. pat. 695,533 [C A., 48, 1016 (1954)].

[51] Arzneimittelfabrik Krewel-Leuffen, Austrian pat 191,878 (1957) (Chem Zentr , 1958, 13359).

[52] Monti and Verona, Gazz. Chim. Ital , 60, 777 (1930) [C A , 25, 1225 (1931)].

[53] Haack, U.S. pat. 2,340,528 [C.A., 38, 4385 (1944)].

[54] Zigeuner, Knierzinger, and Voglar, Monatsh. Chem , 82, 847 (1951)

[55] Zigeuner, Voglar, and Pitter, Monatsh. Chem , 85, 1196 (1954).

the most reactive aromatic systems. Thus heating the trimethylpyrrole 12 in ethanol at refluxing temperature with N-methylolchloroacetamide gave none of the expected amide. Only the dipyrrylmethane 13 was produced, presumably by reaction with formaldehyde derived in turn from cleavage of the N-methylolamide.[17]
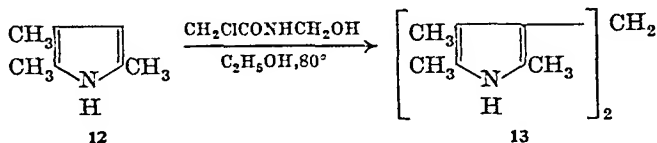
Because of the unusually high reactivity of most methylolamides in strong sulfuric acid and the consequent reduction in selectivity of substitution, many aromatic amidomethylations are complicated by the production of mixtures of isomers and polysubstitution products. For this reason many derivatives formed from substitutions involving equivocal orientations have not yet been characterized adequately. In some instances only the structure of the most readily isolable product in the mixture has been determined. In a few other instances only half-hearted attempts have been made to resolve the mixture; and in still others, particularly where the Tscherniac-Einhorn reaction has been used to introduce basic auxochrome groups into certain aromatic dye structures, little effort to purify products is apparent. However, the modern methods of isolation and characterization that are now available to the organic chemist should serve to remove what has been a formidable barrier to progress in this area.

The characterization of those aromatic amidomethylation products not readily obtainable by independent synthesis has been accomplished in many ways. Perhaps the most common is the direct permanganate[13,56] or dichromate[57] oxidation to a known carboxylic acid, $ArCH_2NHCOR \rightarrow ArCO_2H$. Another method involving two steps is hydrolysis to the benzylamine followed by conversion to a known hydroxymethyl derivative with nitrous acid, $ArCH_2NHCOR \rightarrow ArCH_2NH_2 \rightarrow ArCH_2OH$.[56] A three-step method which can be carried out with only one intervening isolation[57] involves methylation of the benzylamine and hydrogenolysis to a known methylated aromatic compound,[47]

$$ArCH_2NHCOR \rightarrow ArCH_2NH_2 \rightarrow ArCH_2N(CH_3)_2 \rightarrow ArCH_3$$
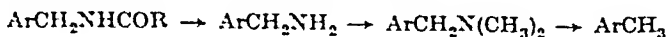
Amidomethylation occurring *ortho* to a functional group often can be diagnosed by subsequent cyclization, although completely unequivocal

[16] O'Connside, *Proc. Roy. Irish Acad.*, 42B, 359 (1935) [*C.A.*, 29, 7326 (1935)].
[17] Truitt and Creagh, *J. Org. Chem.*, 27, 1066 (1962).

identification may not necessarily be achieved thereby. Thus reduction of the product 14 obtained by benzamidomethylation of 4-nitroveratrole gave an amine 15 which could be cyclized to the quinazoline 16 in the presence of phosphorus oxychloride.[58]
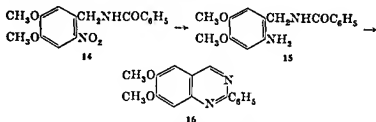
As might be expected, *m*-toluic acid (17) underwent substitution *ortho* to the carboxyl group. The only product isolated (in unspecified yield) from its reaction with N-methylolbenzamide in concentrated sulfuric acid was 6-methylphthalimidine (19) resulting from intramolecular amide interchange of the initial product 18.[7]
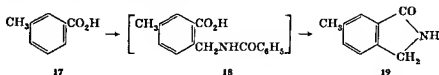
With Formaldehyde and Amides or Nitriles. Few reports of this modification of the Tscherniac-Einhorn reaction have appeared. Buc applied it to the condensation of lactams and imides with some aromatic nitro compounds, using concentrated sulfuric acid as the medium.[31] Thus 4-chloronitrobenzene with equivalent amounts of paraformaldehyde and 4-cyclohexene-1,2-dicarboximide in concentrated sulfuric acid at 65° gave the monosubstitution product 20 in 75% yield.
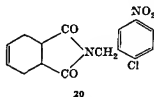
Parris and Christenson used a series of aliphatic and aromatic nitriles, and even hydrogen cyanide, with paraformaldehyde in sulfuric-acetic acid mixtures at temperatures varying from ambient to 90°.[5] Although yields ranged from 20 to 90% most of the aromatic compounds used were

more reactive than benzene.   Bromobenzene, however, with acetonitrile and formaldehyde in concentrated sulfuric acid gave the monosubstitution product p-BrC$_6$H$_4$CH$_2$NHCOCH$_3$ in 37% yield.   In the reaction of acetonitrile and formaldehyde with m-xylene, 85% phosphoric acid at 90° gave a better yield (66% vs. 52%) than a sulfuric-acetic acid mixture at the same temperature.   Of some interest is the successful utilization of acrylonitrile.   With toluene and formaldehyde in a sulfuric-acetic acid mixture at room temperature it afforded the acrylamide

$$p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{NHCOCH}=\text{CH}_2$$
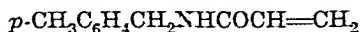
in 89% yield.

Surprisingly, even after heating a mixture of urea, formaldehyde, and 2,4-xylenol in formic acid at 50° for 2 hours, two monomeric urea derivatives 21 and 22 could be isolated.[59]

$$\text{H}_2\text{NCONR}_2 \qquad\qquad \text{RNHCONR}_2$$
$$\textbf{21} \qquad\qquad\qquad\quad \textbf{22}$$
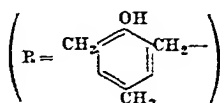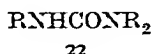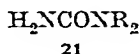
Extension of this reaction to sulfonamides also has been described.[60] Sulfanilamide and its N^4-acetyl derivative were heated with formaldehyde and 4-methyl-2-thiouracil in an acetic-hydrochloric acid mixture.   The products were assigned structure 23 (R = H and CH$_3$CO).
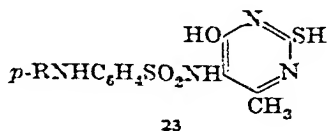
With Ethers of N-Methylol-amides and -imides.   Most of the few reported examples of this condensation involve the diamidomethyl ethers, (RCONHCH$_2$)$_2$O, formed by self-condensation of corresponding methylol-amides.   Thus in his original work Tscherniac was able to condense diphthalimidomethyl ether, [o-C$_6$H$_4$(CO)$_2$NCH$_2$]$_2$O, with phenol, 4-nitro-phenol, and 2-nitrotoluene, using concentrated sulfuric acid.[61]   Zigeuner and co-workers studied the condensations of similar ethers derived from methylolureas.[54]   With anhydrous formic acid at 50°, they obtained the

product 24 from the ether $(C_6H_5NHCONHCH_2)_2O$ and 2,4-xylenol in 90% yield. Under similar conditions the complex ether

$$O(CH_2NHCONHCH_2OH)_2$$

gave the disubstituted urea 25 as the main product together with small amounts of the mono- and tri-substituted ureas 26 and 22, respectively.[62]

RNHCONHC₆H₅   (RNH)₂CO   RNHCONH₂
       24   25   26

$$\left(R = \begin{array}{c} OH \\ CH_3 \diagup \diagdown CH_2- \\ \diagdown \diagup \\ CH_3 \end{array} \right)$$
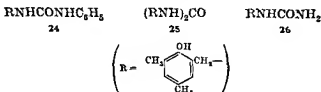
Three reactions involving unsymmetrical ethers have been described. N-Ethoxymethylphthalimide in 100% sulfuric acid at 80–90° gave monosubstituted products with benzene (5% yield) and nitrobenzene (41% yield).[63] A disubstituted product of undetermined structure was obtained when copper phthalocyanine was treated with N-methoxy-methylphthalimide in 100% sulfuric acid at 100°.[64] The corresponding symmetrical diphthalimidomethyl ether at 75° in 100% acid reportedly gave only a monosubstituted derivative.[56]

With N-Halomethyl-amides, -imides, and -carbamyl Compounds. Since its introduction by Cherbuliez and co-workers in 1922,[65,66] this method of amidomethylation has seen comparatively little use. The original workers showed that both functions in 1,4-dichloromethyl-2,5-piperazinedione (27) attack naphthalene and 2-naphthol even in the absence of catalyst.[65] Merely heating the dione 27 with 2-naphthol in benzene under reflux gave 28 (Ar = 2-hydroxy-1-naphthyl) in 89% yield. Although the dichloromethyl derivative 27 was inert to benzene in carbon
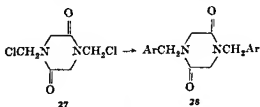
[62] Zigeuner and Pitter, *Monatsh. Chem.*, **86**, 57 (1955).

[63] Tanimoto, Kyo, and Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **65**, 1583 (1962) [*C. A.*, **59**, 503 (1963)].

[64] Rösch and Bayer, Ger. pat. 852,588 (*Chem. Zentr.*, 1953, 8213).

[65] Cherbuliez and Feer, *Helv. Chim. Acta*, **5**, 678 (1922).

[66] Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925).

disulfide, addition of a catalytic amount of anhydrous aluminum chloride gave 1,4-dibenzyl-2,5-piperazinedione (28, Ar = C_6H_5) in 43% yield.[65] More recent work has extended the method to N-substituted N-chloromethylamides, $RCON(R')CH_2Cl$.[32,67] Anhydrous aluminum chloride was the catalytic agent used in most of these studies.[32]

Many of the N-halomethylamides are difficult to isolate and purify. Both N-chloro- and N-bromo-methylphthalimide are, however, fairly stable, but reactive, crystalline solids. For this reason they have been the reagents of choice ever since the former was first used by Herzberg and Lange in 1927.[68] As an example of their high reactivity, it was noted that, when a mixture of 4-chlorophenol, N-chloromethylphthalimide, and a trace of zinc chloride was warmed on the steam bath, spontaneous heating to 130° occurred and the product, 2-phthalimidomethyl-4-chlorophenol, was formed in 70% yield.[69] Similar exothermic behavior was observed in the reaction of N-bromomethylphthalimide with benzene.[14] Indeed, this reagent proved sufficiently reactive to alkylate phenylacetic acid in the presence of zinc chloride catalyst.[47]

Utilization of the high reactivity of N-bromomethylphthalimide for the characterization of alcohols and phenols has been recommended twice.[70,71] Unfortunately, both groups of workers assigned ether structures to their phenolic derivatives. Recent work has demonstrated, however, that reaction of N-bromomethylphthalimide with phenol under their conditions (no catalyst) gave a mixture of o- and p-phthalimidomethylphenols.[15] No N-phenoxymethylphthalimide could be detected in the reaction mixture. Undoubtedly the corresponding derivatives of the other phenols (thymol and β-naphthol) reported by these workers are likewise substituted in the aromatic nucleus.[71]

The N-halomethyl-amides and -imides represent the most strongly electrophilic reagents presently available for the amidomethylation reaction. Recently Olah and co-workers have been able to isolate stable oxocarbonium salts of very strong acids, e.g., $RCO^{\oplus} SbCl_6^{\ominus}$.[72] These are extremely efficient aromatic acylating agents and do not require the presence of Lewis acid catalysts. This suggests that, if a salt such as $o\text{-}C_6H_4(CO)_2NCH_2 SbCl_6^{\ominus}$ could be isolated, i.e., by treatment of N-chloromethylphthalimide with antimony pentachloride, it might serve as a powerful amidomethylating reagent even in the absence of a polarizing catalyst.

A recently developed bifunctional reagent is chloromethylcarbamoyl chloride (29).[73] With β-naphthol in the absence of catalyst it gives 3,4-dihydro-2H-naphtho[1,2-e]-1,3-oxazin-2-one (30) in 25% yield. 2,4-Dichloroaniline gives the analogous nitrogen heterocycle, 3,4-dihydro-6,8-dichloro-2(1H)-quinazolinone (31). Less reactive aromatic compounds such as m-xylene require a zinc chloride catalyst. Chloromethyl isocyanate, ClCH₂NCO, readily obtainable from 29 can be used in its place in these reactions.

$$CH_2O \ + \ HNCO \ \longrightarrow \ HOCH_2NCO \ \xrightarrow[30°]{SOCl_2} \ ClCONHCH_2Cl$$
$$29$$
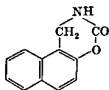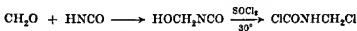
30
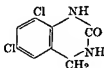
31

With N,N′-Methylene-, -Alkylidene- and -Arylidenebisamides.
The diminished reactivity of these amide derivatives usually requires correspondingly increased reactivity of the nucleophiles. Hence, in the aromatic series, amidoalkylations of this type have usually been restricted to the activated systems: phenols, phenol ethers and esters, and anilines. Three methods have been used to effect condensation. heating the reactants at 190°,[74] warming them at 50° in formic acid,[55] or treating them at 65–130° with phosphorus oxychloride alone or in chloroform.[18,75–78] A single report, however, describes the extension of this reaction to benzene using 100% sulfuric acid as the condensing agent.[63]

The formic acid method is probably the least general. Whereas 1,1′-methylenebis-(3-phenylurea), (C₆H₅NHCONH)₂CH₂, and its p-tolyl analog gave with 2,4-xylenol the unsymmetrical ureas 32,[55] neither N,N′-methylenebisbenzamide, (C₆H₅CONH)₂CH₂,[55] nor N,N′-methylene-bisisovaleramide[54] underwent reaction under these conditions. On the

[73] Hoover, Stevenson, and Rothrock, J. Org. Chem , 28, 1825 (1963).

[74] Štefanović, Bojanović, Vandjel, Maksimović, and Mihailović, Rec. Trav. Chim., 76, 249 (1957).

[75] Ishidate, Sekiya, and Yanaihara, Chem. Pharm. Bull. (Tokyo), 8, 1120 (1960) [C.A , 57, 9736 (1962)].

[76] Sekiya and Yanaihara, Chem. Pharm. Bull. (Tokyo), 7, 746 (1959) [C.A., 54, 16369 (1960)].

[77] Sekiya, Yanaihara, and Masui, Chem. Pharm. Bull. (Tokyo), 9, 945 (1961) [C.A., 57, 16459 (1962)].

[78] Sekiya, Yanaihara, and Masui, Chem. Pharm Bull. (Tokyo), 11, 551 (1963) [C.A 59, 8643 (1963)].

other hand, after only 1 hour at 95°, phosphorus oxychloride caused the

$$CH_3 \underset{\underset{CH_3}{\big|}}{\overset{OH}{\bigcirc}} CH_2NHCONHAr \qquad CH_3 \underset{\underset{CH_3}{\big|}}{\overset{OH}{\bigcirc}} CH_2NHCOC_6H_5$$
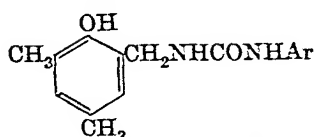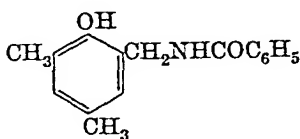
32   (Ar = C₆H₅ or p-CH₃C₆H₄)   **33**

conversion of N,N'-methylenebisbenzamide and 2,4-xylenol to the expected product **33** in 93% yield.[75]   Dilute mineral acid catalysis appears to be useless in these reactions.   Treatment of 2-naphthol with several methylenebisamides, $(RCONH)_2CH_2$, in ethanolic hydrochloric acid led to the methylenebisnaphthol **34** instead of the expected amidomethylation products.[79]

$$\left[\bigcirc\!\!\!\bigcirc \text{—}\atop{OH} \right]_2 CH_2 \qquad \left[HO\text{—}\bigcirc\!\!\!\bigcirc \right]_2 CHC_6H_5$$

34   **35**

$$\bigcirc\!\!\!\bigcirc \overset{CH(C_6H_5)NHCOCH_3}{\underset{OH}{}}$$
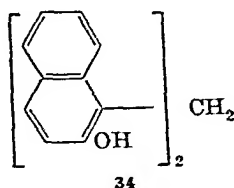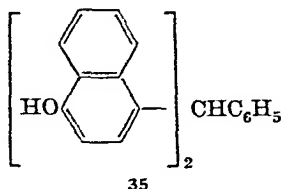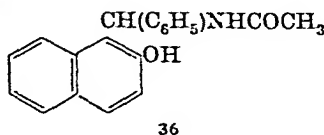
36

A by-product, **35**, of similar character was obtained when benzylidene-bisacetamide, $(CH_3CONH)_2CHC_6H_5$, was heated 4 hours at 190° with 1-naphthol.[74]   In contrast, 2-naphthol, under the same conditions, gave the α-amidoalkylation product, **36**, in 93% yield.[74]   This tendency for the thermal (190°) reaction to substitute *ortho* rather than *para* to the oxygen function is further supported by the observation that benzylidene-bisacetamide with 2,4-xylenol gave the *ortho* derivative **37** in 74% yield but the *para* isomer **38** from 2,6-xylenol in 30% yield.[74]   Furthermore, reactions of benzylidenebisacetamide and benzylidenebisbenzamide with phenol, phenyl acetate, and phenyl benzoate (all at 190°) led to *o*-mono-

$$CH_3 \underset{\underset{CH_3}{\big|}}{\overset{OH}{\bigcirc}} CH(C_6H_5)NHCOCH_3 \qquad CH_3 \underset{\underset{CH(C_6H_5)NHCOCH_3}{\big|}}{\overset{OH}{\bigcirc}} CH_3$$
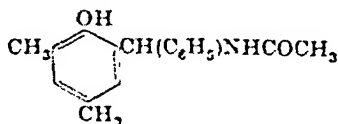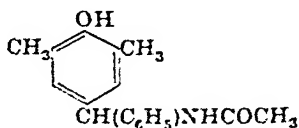
37   **38**

amidoalkylated derivatives as the only isolable products, albeit in poor to moderate yields (12–69%).[74]

The phosphorus oxychloride method is less selective but considerably more effective in bringing about condensation. Thus treatment of phenol and N,N'-methylenebisacetamide with phosphorus oxychloride in chloroform for 4 hours under reflux gave a mixture of equal amounts of o- and p-acetamidomethylphenol.[77] By using various reaction temperatures and times, excellent yields were obtained from a number of other aromatic compounds. These included 4-nitrophenol (85%), 4-methoxytoluene (93%), and 2-methylacetanilide (86%).[18] Other yields ranged from 71 to 98%.[18,75]

The thermal (190°) condensation method was found not to require the preformed bisamide reagent.[74] Thus heating a mixture of benzaldehyde, acetamide, and p-cresol at 190° for 4 hours gave the alkylated product 39 in 58% yield. The use of preformed benzylidenebisacetamide gave a

$$C_6H_5CHO + CH_3CONH_2 + p\text{-}CH_3C_6H_4OH \xrightarrow{190°}$$

39
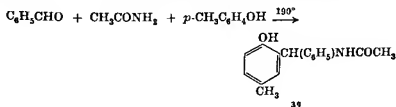
lower yield, 43%. However, in most other instances the preformed reagent led to distinctly better yields.[74]

Related to these amidoalkylations is an interesting condensation reported by Pirrone in 1937.[80] He found that 8-hydroxyquinoline treated with two equivalents of benzaldehyde and one of an amide (formamide, acetamide, benzamide, or salicylamide) in warm (60–80°) ethanol or benzene gave 3-acyl derivatives of 2,4-diphenyl-2-pyrido [3,2-λ][1,3]benzoxazine (40, R = H, CH₃, C₆H₅, or o-HOC₆H₄).

40
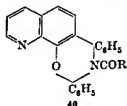
The use of an unsymmetrical methylene-bisamide has been reported once.[63] Treatment of benzene with N-benzamidomethylphthalimide in

⁸⁰ Pirrone, Gazz. Chim. Ital., 67, 529 (1937) [Chem. Zentr., 1938, I, 1581] [C.A., 32, 1701 (1938)].

100% sulfuric acid at 90° gave N-benzylphthalimide in 24% yield. No N-benzylbenzamide was isolated.

With N-Aminomethyl-amides and -imides. Compounds of this type, e.g., $RCON(R'')CH_2NR_2'$, do not amidomethylate directly at a carbon atom of an aromatic system. Rather, they cleave as indicated $RCON(R'')-|-CH_2NR_2$ and thus behave as *amino*methylating agents. A special reaction of indole is known, however, in which the end result is the same as if an amidomethylation had occurred.

When equivalent amounts of indole and N-piperidinomethylphthalimide (41) were heated under reflux for 9 hours in xylene containing a little powdered sodium hydroxide, 3-phthalimidomethylindole (42) was isolated in 48% yield.[81] When the reaction was interrupted after 1–2 hours,
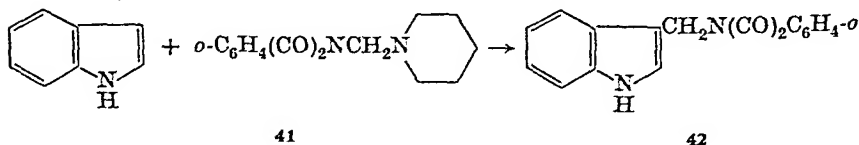
however, N-skatylpiperidine (43) was obtained in 50% yield. The latter compound was converted smoothly to 42 by further treatment with phthalimide. Thus the aminomethylation product 43 was formed first; but on prolonged treatment it reacted further with the phthalimide present, probably by an elimination-addition mechanism involving 44,
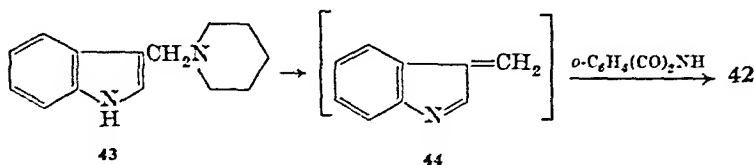
typical of alkylation reactions of gramine.

N-Piperidinomethylbenzenesulfonamide condensed with indole in the same way to give 45, but in only 21% yield.[82] N-Dimethylaminomethylbenzamide, however, amidomethylated the nitrogen atom of indole.[63]
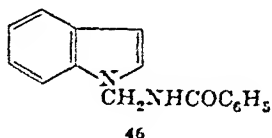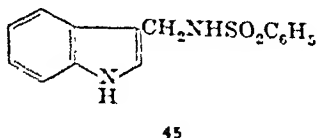
No further reaction could be induced, and the monosubstituted product 46 was isolated in 57% yield. Supposedly the methylene imide, CH_2=$NCOC_6H_5$, is the intermediate in this reaction and the NH group is the only function in indole sufficiently reactive to add to it. Attempts to force substitution at the 3-position of indole by using media acidic enough presumably to form the stronger electrophile $\overset{\oplus}{CH_2}NHCOC_6H_5$ led only to decomposition of the acid-sensitive substrate.[83]

With Amidomethanesulfonic Acids. Only two reactions of this type have been described.[63] Both involved the use of sodium benzamidomethanesulfonate (47) as the reagent. With benzene in 100% sulfuric acid at 95°, N-benzylbenzamide was isolated in 62% yield. With nitrobenzene under similar conditions N-(m-nitrobenzyl)benzamide was obtained, but in only 8% yield.

$$C_6H_5CONHCH_2SO_3Na + ArH \rightarrow C_6H_5CONHCH_2Ar$$
$$\underset{47}{}$$
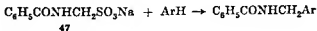
With N-Acylimines. Only one example of this type of reaction has been found. Ivanoff treated N-benzoyldiphenylketimine with phenylmagnesium bromide and obtained N-benzoyltritylamine in 62% yield.[19]

$$C_6H_5CON=C(C_6H_5)_2 \xrightarrow{C_6H_5MgBr} C_6H_5CONHC(C_6H_5)_3$$
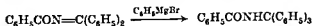
α-Amidoalkylation of Aliphatic Carbon Atoms

With N-Methylol and N-α-Alkylol Derivatives of Amides, Imides, and Carbamyl Compounds. The extension of the Tscherniac-Einhorn reaction to the aliphatic series is limited by the side reactions that aliphatic compounds undergo in strong acid media. The nucleophiles successfully employed possess active hydrogen atoms on aliphatic carbon atoms and would be expected to exhibit a wide range of nucleophilic activity.

Several attempts to amidomethylate malonic ester with N-methylolbenzamide and N-methylolphthalimide in sulfuric acid have failed.[84,85] Monti succeeded, however, in benzamidomethylating 1-phenylpropane-1,3-dione and 1,3-diphenylpropane-1,3-dione, although no yields were given.[86] Hellman and co-workers, using the same substrates as well as pentane-2,4-dione, 5,5-dimethylcyclohexane-1,3-dione, and 1,2-diphenyl-pyrazolidine-3,5-dione with N-methylolphthalimide in concentrated sulfuric acid, were able to prepare the amidomethylated products in about

[84] Buc, *J. Am. Chem. Soc.*, **69**, 254 (1947).
[85] Hellmann, Aichinger, and Wiedemann, *Ann.*, **626**, 35 (1959).
[86] Monti, *Gazz. Chim. Ital.*, **60**, 39 (1930) [*C.A.*, **24**, 4013 (1930)].

80% yields.[85] The alkylated derivatives 48 and 49 are examples of the products obtained.
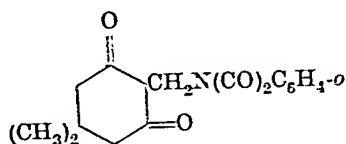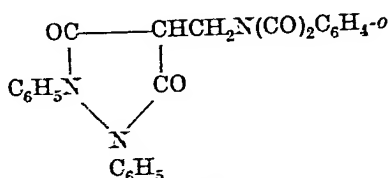
48   49

The reaction conditions usually employed, i.e., concentrated sulfuric acid, do not seem to be generally applicable, although admittedly they have been studied only to a limited extent. The reaction of N-methylolbenzamide with cyclohexane-1,3-dione is reported to give the amidomethylated diketone 50 in 36% yield with concentrated sulfuric acid; in 20% yield with ethanol and hydrochloric acid; in 40% yield with acetic acid and zinc chloride; and in 65% yield with acetic acid and boron
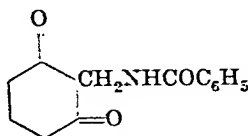
50

trifluoride etherate.[85] By using boron trifluoride etherate, a 74% yield of the ketone $C_6H_5CONHCH_2CH(COC_6H_5)_2$ was obtained from the condensation of 1,3-diphenylpropane-1,3-dione with N-methylolbenzamide. The latter reaction conditions appear to provide a serviceable alternative to the use of concentrated sulfuric acid.

A series of reactions with trinitromethane as the nucleophile was carried out successfully using N-methylolurethan and a variety of N-methylolamides.[87,88] An example is the reaction of trinitromethane with N-methylolmethacrylamide in water to give the amide

$$CH_2=C(CH_3)CONHCH_2C(NO_2)_3$$
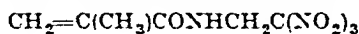
in 87% yield. Yields were not given for all the reactions, but those reported were above 80%. With these compounds water often served as the solvent, and the condensation occurred readily over a wide range of pH (<7).

An interesting reaction has been reported in which 2-hydroxypteridine hydrate (51) was condensed with four different active methylene compounds (pentane-2,4-dione, ethyl acetoacetate, diethyl malonate, and

ethyl cyanoacetate) in 75, 80, 90, and 90% yields, respectively, to give compounds of structure 53.[89] Since the reactions were conducted in

$(R = CH_2COCH_3, CH_2COCH_2CO_2C_2H_5, -CH(CO_2C_2H_5)_2, NCCHCO_2C_6H_5)$
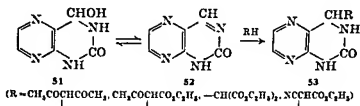
neutral or basic media, it is likely that they proceed by a Michael-type addition of enolate anion to the pteridine 52 rather than directly through the hydrate 51.

Only a few reactions of N,N'-dimethylol compounds have been reported.[87] N,N'-Dimethylolfumaramide and trinitromethane in water at pH 0.8 gave the fumaramide 54 in 48% yield. A patent describes the reaction of trinitromethane with N,N'-dimethylolurea and with a urea–

$$(O_2N)_3CCH_2NHCOCH$$
$$HCCONHCH_2C(NO_2)_3$$
$$54$$
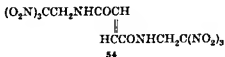
formaldehyde mixture to give $CO(NHCH_2C(NO_2)_3)_2$ in 77% and 88% yields, respectively.[88] The condensation of acetylene with N,N'-dimethylolurea to give N-methylol-N'-2-propynylurea is mentioned.[90]

With Formaldehyde or Acetaldehyde and Sulfonamides. Alkyl- and aryl-sulfonamides with formaldehyde and alkali cyanides give products of the type RSO_2NHCH_2CN. Reaction of benzenesulfonamide and acetaldehyde with potassium cyanide yields the analogous derivative, $C_6H_5SO_2NHCH(CH_3)CN$.[91]

Sulfanilamide and paraformaldehyde condense at elevated temperature with 2-picoline to give the product 55. Similar reactions occurred to give amidomethylated products from quinaldine, 9-methylacridine, 9-ethylacridine (i.e., 56), and 2-methyl-4(3H)-quinazolinone (i.e., 57).[92] Indication that amidomethylation occurred on the methyl group of 2-methyl-4(3H)-quinazolinone and not on the amide nitrogen atom was

[89] Albert and Howell, J. Chem. Soc., 1962, 1591.
[90] Reppe, Keyssner, and Hecht, Ger. pat. 724,759 [C.A., 37, 5733 (1943)]. Fr. pat 839,875 [Chem. Zentr., 1939, II, 734].
[91] Reuter, Ger. pat. 847,006 [C.A., 50, 2669 (1956)].
[92] Monti and Felici, Gazz. Chim. Ital., 70, 375 (Chem. Zentr., 1940, II, 2158).

derived from the fact that no reaction took place with 4(3*H*)-quinazolinone, in which the 2-methyl group is absent. In contrast, N-methylolbenzamide

55

56

57

$(R = p\text{-}H_2NC_6H_4SO_2NHCH_2\text{—})$
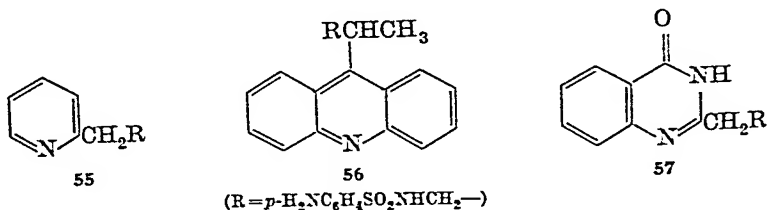
and 2-methyl-4(3*H*)-quinazolinone reportedly condense preferentially at the 3-nitrogen atom.[92a]

With Ethers and Esters of N-Methylol- and N-α-Alkylol-amide Derivatives. Most of the reported work in this area is concerned with the reaction of trinitromethane with N-benzoxymethyl-acrylamide and -methacrylamide, $CH_2{=}C(R)CONHCH_2OCOC_6H_5$ ($R = H, CH_3$).[93] Both polar and non-polar solvents have been used with equally favorable results. Regardless of solvent, amidomethylation with the acrylamide derivative ($R = H$) occurred with concomitant addition of trinitromethane to the carbon-carbon double bond to produce the hexanitro compound $(O_2N)_3CCH_2CH_2CONHCH_2C(NO_2)_3$. That addition to the carbon-carbon double bond was faster than the ester cleavage was indicated by the observation that, with one equivalent of trinitromethane, the principal product was the adduct $(O_2N)_3CCH_2CH_2CONHCH_2OCOC_6H_5$. Trinitromethane did not add to the methacrylamide ($R = CH_3$). The same workers examined the reaction of trinitromethane with N,N'-diacetoxymethyl- and N,N'-dibenzoxymethyl-fumaramide and reported a 2% and 47% yield, respectively, of the product **54**. Since water was the solvent for the reaction of the N,N'-diacetoxy compound, the formation of the fumaramide **54** may occur by a mechanism different from that involving the dibenzoate. The latter reaction was carried out under anhydrous conditions.

The trichloromethyl derivative **58** reacted with potassium cyanide to give the unsaturated nitrile **59** in 53% yield.[94] Elimination-substitution reactions of this type take place in a number of reactions with alkali cyanides. The reactions are described on pp. 82–83. In the same article it was reported that the unsaturated trichloromethyl derivative **60** and the

$$C_2H_5O_2CNHCH(OCOCH_3)CCl_3 \xrightarrow{\text{KCN}} C_2H_5O_2CNHC(CN){=}CCl_2$$

58　　　　　　　　　　　　　　　　　　　**59**
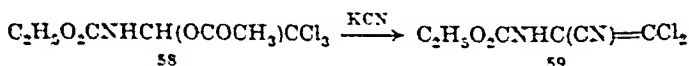
potassium salt of diethyl malonate gave the triethyl ester **61** in 35% yield.   It was later shown, however, that **60** was actually the symmetrical

$$C_2H_5O_2CN{=}CHCCl_3 \; + \; K[CH(CO_2C_2H_5)_2] \rightarrow$$

<div align="center">60</div>

$$C_2H_5O_2CNHCH[CH(CO_2C_2H_5)_2]CCl_3$$

<div align="center">61</div>
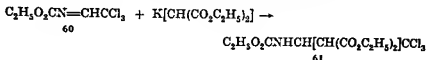
ether **62**.[95]   This reaction, therefore, appears to be the only one in which an ether has been utilized, albeit unknowingly, as an α-amidoalkylating agent of an aliphatic carbon atom.

$$(C_2H_5O_2CNHCHCCl_3)_2O$$

<div align="center">62</div>
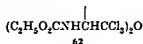
With N-Halomethyl- and N-α-Haloalkyl-amide Derivatives. The N-halomethyl- or N-α-haloalkyl-amides are the reagents of choice for the amidoalkylation of aliphatic compounds,[33,96–101] in contrast to the aromatic series where N-alkylolamides are more commonly employed. The halomethylamides often are prepared just before use and, with little or no purification, are added to the alkali metal derivative of the active methylene compound suspended in some inert solvent.   Many structural types have been utilized.   A partial list would include malonic esters and their monosubstituted derivatives, cyclic and acyclic β-diketones, cyano-acetic esters, acetoacetic esters and their monosubstituted derivatives, and nitroacetic ester.   Reported yields exhibit wide ranges.

No systematic investigation of the important reaction conditions is available, but the N-halomethyl derivatives of aliphatic amides generally give lower yields than do N-halomethylbenzamides and N-halomethyl-phthalimides.   For example, diethyl methylmalonate condenses with N-chloromethylformamide, with N-chloromethylacetamide, with N-chloromethylbenzamide, and with N-chloromethylphthalimide in 20, 31, 77, and 81% yields, respectively.[97,100]

With N-chloro- and N-bromo-methylphthalimide, monosubstituted derivatives of active methylene compounds appear to react more smoothly than do unsubstituted ones.   The amidomethylation product **63** was not obtained from N-bromomethylphthalimide and the sodium derivative of diethyl malonate in benzene.   Instead, the tetra ester **64**, phthalimide,

[93] Feist, *Ber.*, **45**, 945 (1912).
[94] Böhme, Broese, Dick, Eiden, and Schunemann, *Chem. Ber.*, **92**, 1599 (1959).
[95] Böhme, Broese, and Eiden, *Chem. Ber.*, **92**, 1258 (1959).
[96] Böhme, Dick, and Driesen, *Arch. Pharm.*, **294**, 312 (1961).
[97] Böhme and Eiden, *Arch. Pharm.*, **292**, 642 (1959).
[100] Böhme and Eiden, Ger. pat. 1,025,883 [*C.A.*, **54**, 9773, (1960)].
[101] Böhme, Eiden, and Schunemann, *Arch. Pharm.*, **294**, 307 (1961)

and sodium bromide were formed.[102] This result is compatible with the

$$o\text{-}C_6H_4(CO)_2NCH_2CH(CO_2C_2H_5)_2 \qquad CH_2[CH(CO_2C_2H_5)_2]_2$$

63   **64**
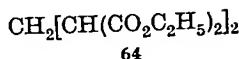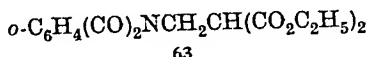
observation that phthalimide is cleaved from 2-phthalimidomethylcyclo-
hexane-1,3-dione in the presence of excess active methylene compound
to produce methylenebiscyclohexane-1,3-dione **65**.[103] In both reactions
it seems likely that a second molecule of the enolate ion displaces a
phthalimide anion (e.g., from **63**), giving the observed products.

65
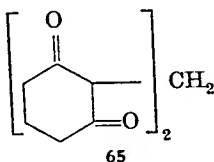
Failure to obtain the normal substitution product from N-bromomethyl-
phthalimide and sodioacetoacetic ester also has been reported.[104] In
contrast, good yields have been obtained from the reaction of N-chloro-
methylphthalimide with the sodium derivatives of many *monosubstituted*
active methylene compounds;[97] and the amidomethylated compound **66**
has been prepared in 73% yield from N-bromomethylphthalimide and
the sodium salt of 3-phenylbenzofuran-2-one.[105]

66
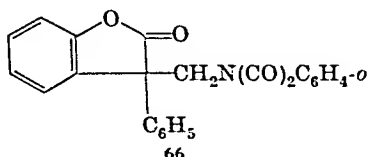
An interesting set of reactions has been reported in which various
substituted aromatic α-haloalkylamides of the type $ArCONHCHClCCl_3$
are treated in dry acetone with 2 moles of potassium cyanide to give, not
the simple substitution products, but products of the type

$$ArCONHC(CN){=}CCl_2$$

67
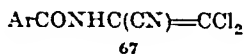
[102] Vinkler and Szabó, *Magy. Kem. Folyoirat.* **56**, 209 (1950) [*C.A.*, **45**, 7984 (1951)];
published in Russian in *Acta Chim. Hung.*, **1**, 103 (1951) [*C.A.*, **46**, 2500 (1952)].
[103] Hellmann and Aichinger, *Chem. Ber.*, **92**, 2122 (1959).
[104] Pucher and Johnson, *J. Am. Chem. Soc.*, **44**, 817 (1922).
[105] H. E. Zaugg and R. W. De Net, unpublished data.

in which elimination has occurred as well.[106,107] One mole of potassium cyanide reacts rapidly, but no pure product can be isolated. Apparently the second mole of cyanide dehydrochlorinates the initially formed substitution products to the more readily isolable unsaturated nitriles 67. The yields of the nitriles 67 are only fair, but their hydrolysis to the corresponding acids can be achieved in essentially quantitative yields.

With N,N'-Methylenebisulfonamides and N,N'-Ethylidenebisurethan or Their Precursors. Only a few successful reactions of this type have been described.[85,108] In general, N,N'-alkylidenebisamides fail to undergo amidomethylation with active methylene compounds[109,110] Instead they give the corresponding alkylidene derivatives, i.e., RCH(CHX₂)₂, analogous to the methylenebis compounds 64 and 65.

The condensation of cyclohexane-1,3-dione in sulfuric acid with N,N'-methylenedibenzenesulfonamide or N,N'-methylenedi-p-toluenesulfonamide yielded the corresponding diketones 68 in 18 and 19% yields, respectively.[85]

$C_2H_4OCONHCH(CH_3)CH(COCH_3)_2$
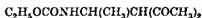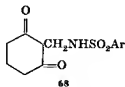
68   69

Ethyl carbamate, acetaldehyde, and pentane-2,4-dione were condensed to give the urethan 69.[108] This is apparently the only reported case of amidoalkylation with an alkylidenebisamide derivative.

With N,N'-Arylidenebisamides or Their Precursors. The reactivity of these amide derivatives though diminished is still sufficient for condensation with most of the reactive methylene compounds. Two methods are generally used to effect the condensation: the preformed arylidenebisamide is condensed with the active methylene compound, or the aldehyde and amide (or the ammonium salt of the corresponding carboxylic acid) are treated with the active methylene compound. Both methods usually involve acetic anhydride or acetic acid-acetic anhydride mixtures as the solvent, although early workers used ethanol and hydrochloric acid.[108,111]

[106] Hirwe and Deshpande, *Proc. Indian Acad., Sci.* 13A, 277 (1941) [*C.A.*, 35, 6250 (1941)]

[107] Hirwe and Rana, *J. Indian Chem. Soc.* 17, 481 (1940) [*C.A.* 35, 2130 (1941)]

[108] Bianchi, *Gazz. Chim. Ital.*, 42 (I), 499 (1912) (*Chem. Zentr.*, 1912, II, 329).

[109] Stefanović, Prekajski, and Mihailović, *Ber. Chem. Ges. Belgrade*, 22, 113 (1957) (*Chem. Zentr.*, 1959, 9883).

[110] Stefanović, Stefanović, and Milanović, *Ber. Chem. Ges. Belgrade*, 20, 313 (1955) (*Chem. Zentr.*, 1957, 6134).

[111] Bianchi and Schiff, *Gazz. Chim. Ital.*, 41 (II), 81 (1911) (*Chem. Zentr.*, 1911, II, 1919).

The condensation of arylidenebisamides with ethyl nitroacetate clarified the reaction course. It was shown that, when a mixture of benzaldehyde, acetamide, and ethyl nitroacetate in acetic anhydride was heated, the ester 70 was obtained in 61% yield.[112] The course of the reaction was the same when N,N'-benzylidenebisacetamide was substituted for the benzaldehyde and acetamide. Under the latter conditions, however, a better yield (85%) of 70 was obtained.

$$C_6H_5CH(NHCOCH_3)_2 + O_2NCH_2CO_2C_2H_5 \xrightarrow{(CH_3CO)_2O}$$
$$CH_3CONHCH(C_6H_5)CH(NO_2)CO_2C_2H_5 + CH_3CONH_2$$
$$70$$
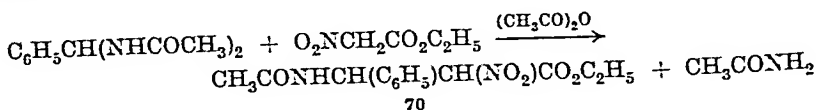
N,N'-Benzylidenebisacetamide also condensed with nitromethane in analogous fashion, producing the nitro compound

$$CH_3CONHCH(C_6H_5)CH_2NO_2$$
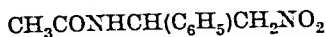
in 32% yield.[113] As expected, nitromethane is less reactive than ethyl nitroacetate and requires a longer reaction time even for lower yields.

Ethyl acetoacetate has been condensed with aldehydes and amides in ethanol and hydrochloric acid[111] as well as with N,N'-arylidenebisamides in acetic anhydride.[114] Compounds of the type

$$RCONHCH(Ar)CH(COCH_3)CO_2C_2H_5$$

are obtained. Like acetoacetic ester itself, the condensation products exist in two tautomeric forms. As a consequence, they decolorize bromine water and produce a reddish brown coloration with alcoholic ferric chloride solution. Acid cleavage leads to β-aryl-β-acylaminopropionic acids, $RCONHCH(Ar)CH_2CO_2H$, in good yields, but ketone cleavage does not occur.

The reaction of arylidenebisamides with malonic esters in acetic anhydride yields the expected condensation products.[115]

$$RCONHCH(Ar)CH(CO_2R')_2$$
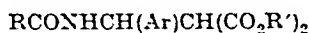
The reaction time appears to be important. For example, N,N'-benzylidenebisacetamide gives a 62% yield of amidoalkylated product in 3 hours, but after 9 hours only an 11% yield can be obtained. The major products isolated from these prolonged reactions are the arylidenemalonic esters $ArCH=C(CO_2R')_2$ resulting from the elimination of amide. Partial

hydrolysis of the amidoalkylated esters produces the malonic acids which decarboxylate to give β-aryl-β-acylaminopropionic acids

$$RCONHCH(Ar)CH_2CO_2H$$
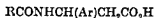
in excellent yields.[115] Diethyl ethylmalonate reacts with N,N'-benzylidenebisacetamide in an analogous fashion. Although partial hydrolysis of the product leads to a half-ester of malonic acid, more severe conditions result in both decarboxylation and amide elimination to give α-ethylcinnamic acid, $C_6H_5CH=C(C_2H_5)CO_2H$.[115]

Reactions of cyanoacetic esters with arylidenebisamides do not take the expected course but lead to the elimination products $ArCH=C(CN)CO_2R$.[116] These condensations proceed best in the absence of any solvent or catalyst.

Hippuric acid as an active methylene compound condenses with arylidenebisamides in glacial acetic acid or in acetic anhydride to give, as the main product, β-aryl-α,β-diacylaminopropionic acids, 73, in two diastereomeric forms.[117] In several reactions the corresponding azlactones 72 are formed; and in all instances small amounts (~10%) of the

$$C_6H_5CONHCH_2CO_2H \xrightarrow{(RCONH)_2CHAr}$$

71

72   73
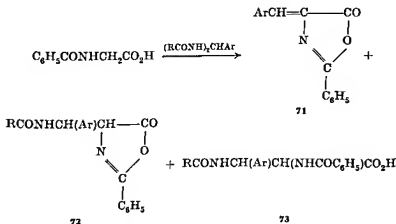
azlactones 71 of β-arylacrylic acids are obtained. The complicated configurational relationships among these products have not been completely elucidated. Hippuric acid does not react with o- or p-nitrobenzylidenebisacetamide, but the *meta* isomer gives the corresponding azlactone 71 (Ar = m-O₂NC₆H₄).[117] The acids 73 as well as the azlactones 72 undergo acid hydrolysis to the corresponding β-aryl-α,β-diaminopropionic acids, $ArCH(NH_2)CH(NH_2)CO_2H$.

[115] Stefanović and Nikić, *J. Org. Chem.*, 17, 1305 (1952).
[117] Stefanović and Stefanović, *J. Org. Chem.*, 21, 161 (1956).

One heterocyclic compound which has been reported[109] to undergo reaction in acetic anhydride with N,N'-benzylidenebisacetamide is piperazine-2,5-dione. It gives the diketone **74** in 29% yield. Other heterocyclic compounds apparently condense with N,N'-benzylidenebis-

$$CH_3CONHCH(C_6H_5)\ \begin{array}{c} COCH_3 \\ N \\ \\ O= \\ N \\ COCH_3 \end{array} =O$$

74
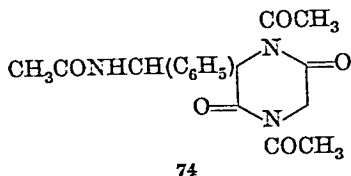
acetamide in glacial acetic acid but without leading to α-amidoalkylation products.[109,110] Thus rhodanine gives **75** in 99% yield,[110] and barbituric acid gives **76** in 91% yield.[109] The yield of the latter is lowered to 51% when the solvent is acetic anhydride.

$$\begin{array}{c} NH \\ S=C \quad C=O \\ | \quad | \\ S——C=CHC_6H_5 \end{array}$$

$$\begin{array}{c} NH \\ O=C \quad C=O \\ | \quad | \\ HN \quad C=CHC_6H_5 \\ C \\ || \\ O \end{array}$$

75   **76**
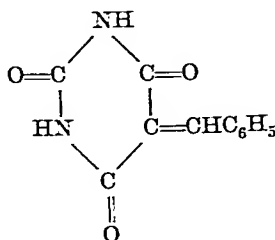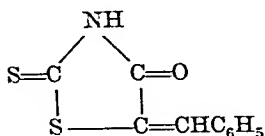
Some cyclic β-diketones are reported to condense with N,N'-benzylidenebisamides to give the corresponding 2-(α-acylaminobenzyl) derivatives in poor to moderate yields.[85] For example, 5,5-dimethylcyclohexane-1,3-dione, with N,N'-benzylidenebisacetamide, produces **77** in 12% yield. In the same manner cyclohexane-1,3-dione and N,N'-benzylidenebis-benzamide give the corresponding product **78** in 40% yield.

$$\begin{array}{c} O \\ \| \\ CH(C_6H_5)NHCOCH_3 \\ (CH_3)_2 \qquad =O \end{array}$$

$$\begin{array}{c} O \\ \| \\ CH(C_6H_5)NHCOC_6H_5 \\ =O \end{array}$$

77   **78**
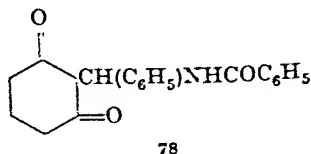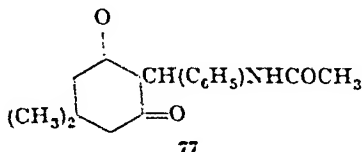
With N-Aminomethylamides and Their Quaternary Salts.

In contrast to the aromatic systems, a number of reactive methylene compounds undergo base-catalyzed amidomethylation with N-dialkyl-aminomethylamides.[51,118] They include dialkyl malonates and their

[119] Hellmann and Haas, *Chem. Ber.*, **90**, 1357 (1957).

monosubstituted derivatives, ethyl acetoacetate, β-diketones, and nitrocyclohexane. For example, the last compound condenses with N-(dimethylaminomethyl)benzamide 79 in the presence of powdered sodium hydroxide in boiling toluene to give 80 in 38% yield.[118]

$$C_6H_5CONHCH_2N(CH_3)_2 + \underset{NO_2}{\text{(cyclohexane)}} \xrightarrow[C_6H_5CH_3]{NaOH}$$

79

$$\underset{80}{O_2N \text{(cyclohexane)} CH_2NHCOC_6H_5} + (CH_3)_2NH$$
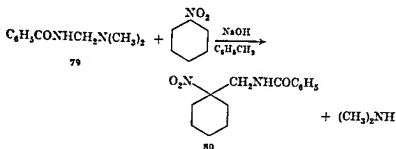
Two cyano compounds have been amidoalkylated by N-diethylaminomethylbenzamide with good results.[118] Diethyl α-cyanomalonate (81) reacts in the expected manner to give an 85% yield of the product 82, and ethyl α-phenylcyanoacetate undergoes analogous conversion in 74%

$$C_6H_5CONHCH_2N(C_2H_5)_2 + \underset{(CH_2)_4CO_2C_2H_5}{\overset{CN}{\underset{|}{CHCO_2C_2H_5}}} \xrightarrow[C_6H_5CH_3]{NaOH}$$

81

$$C_6H_5CONHCH_2\underset{(CH_2)_4CO_2C_2H_5}{\overset{CN}{\underset{|}{CCO_2C_2H_5}}}$$

82
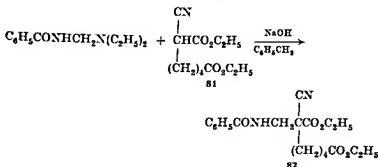
yield. In interesting contrast, however, is the observation that compound 81 with *N-methylolbenzamide* in strong acid is converted to the N-alkylated product 83 in high yield.[84,119]

$$C_6H_5CONHCH_2NHCOCH(CO_2C_2H_5)(CH_2)_4CO_2C_2H_5$$

83
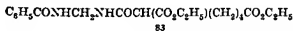
Only a few reactions of N-dialkylaminomethylphthalimides with reactive methylene compounds have been reported, and they have usually led to by-products.[81] Diethyl malonate reacts with N-dimethylaminomethylphthalimide (84) to yield the unstable derivative 85. The chief products formed were phthalimide and diethyl methylenemalonate (86). Attempts to add phthalimide to 86 to produce 87 were not successful.

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[118] English and Clapp, *J. Am. Chem. Soc.*, **67**, 2262 (1945).

On the contrary, evidence indicated that, under the reaction conditions, 87, like 85, undergoes elimination to give 86.

$$o\text{-}C_6H_4(CO)_2NCH_2N(CH_3)_2 \; + \; CH_2(CO_2C_2H_5)_2 \xrightarrow{\;NaOH\;} (CH_3)_2NCH_2CH(CO_2C_2H_5)_2$$

<div align="center">84   85 $\Big\downarrow$ $-(CH_3)_2NH$</div>

$$o\text{-}C_6H_4(CO)_2NCH_2CH(CO_2C_2H_5)_2 \xrightarrow{-[o\text{-}C_6H_4(CO)_2NH]} CH_2{=}C(CO_2C_2H_5)_2$$

<div align="center">87   86</div>
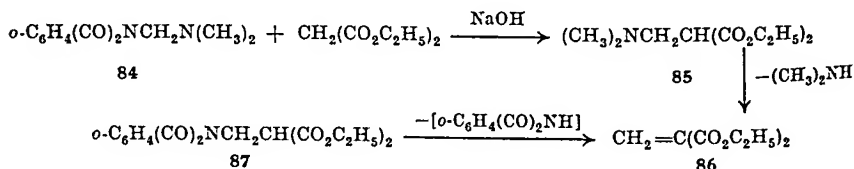
The quaternary salt 88 reacted with diethyl malonate to give only a small amount of the dialkylated product 89.[81] With sodium cyanide, however, it gave the nitrile $o\text{-}C_6H_4(CO)_2NCH_2CN$ in 80% yield.

$$o\text{-}C_6H_4(CO)_2NCH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} \; + \; CH_2(CO_2C_2H_5)_2 \xrightarrow[C_2H_5OH]{NaOC_2H_5}$$

<div align="center">88</div>

$$[o\text{-}C_6H_4(CO)_2NCH_2]_2C(CO_2C_2H_5)_2$$

<div align="center">89</div>
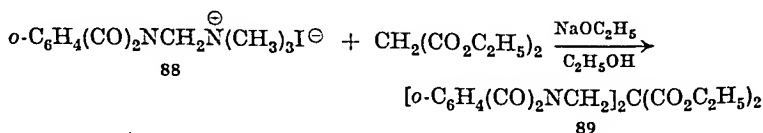
With N-Acylimines. Relatively few examples of this reaction have been reported. Ivanoff found that benzoyl derivatives of diaryl ketimines will add reactive nucleophilic agents such as the chloromagnesium derivative of sodium phenylacetate[19] and the lithium derivatives of acetonitrile,[120] propionitrile,[121] and butyronitrile[121] prepared *in situ* with lithium amide in liquid ammonia.
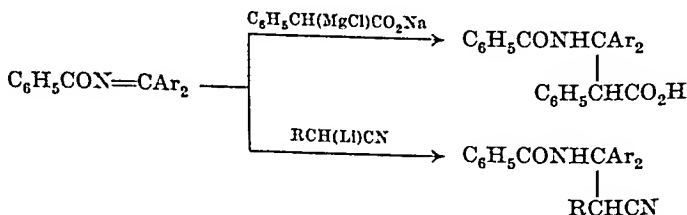
Yields of the reactions ranged between 40 and 85%. This synthesis offers promise as a convenient entry to systems highly substituted by bulky groups.

α-Amidoalkylation of Ethyl Acetoacetate with N,N′-Alkylidene- and N,N′-Arylidene-bisureas or Their Precursors. The Biginelli Pyrimidine Synthesis. Biginelli treated ethyl acetoacetate with urea

[119] Ivanoff, Markov, and Dobrev, *Compt. Rend. Acad. Bulgare Sci.,* 15, 403 (1962) [C.A., 60, 4112 (1964)].

[121] Ivanoff, Konstantinova, and Popandova, *Compt. Rend. Acad. Bulgare Sci.,* 15, 617 (1962) [C.A., 59, 2699 (1963)].

and benzaldehyde and obtained 5-carbethoxy-2-keto-6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine (90).[122] He extended the reaction to other

$$CH_3COCH_2CO_2C_2H_5 + C_6H_5CHO + CO(NH_2)_2 \rightarrow$$

90
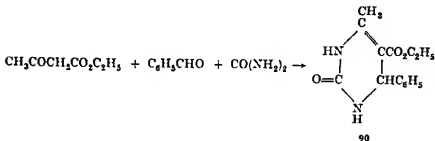
aldehydes and made the first contribution to an understanding of the course of the reaction by using the corresponding arylidenebisureas, $(H_2NCONH)_2CHAr$, in place of the aldehydes and urea.[122-124] Under the original conditions the reaction gave only moderate yields, but later workers, by using a 1-mole excess of ethyl acetoacetate, were able to increase the yields appreciably.[125] Using benzaldehyde, they also showed that the substituted dihydrolutidine 91 was a by-product and that the

91
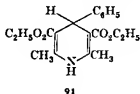
course of the synthesis can be described as follows. Preformed N,N′-benzylidenebisurea reacts with ethyl acetoacetate to give 90. The molecule of urea which is eliminated in this process condenses with a second molecule of ethyl acetoacetate to give ethyl β-ureidocrotonate, $CH_3C(NHCONH_2){=}CHCO_2C_2H_5$, which in turn reacts with benzaldehyde to give the Biginelli product 90. However, some of the ureidocrotonate hydrolyzes to ethyl β-aminocrotonate, ammonia, and carbon dioxide In the presence of ammonia, conditions become favorable for the Hantzsch synthesis and this accounts for the side reaction leading to the pyridine derivative 91.

Further work confirmed these results and showed that (a) condensation of urea with ethyl α-benzylideneacetoacetate plays no part in the reaction; and (b) that under the reaction conditions the ureidocrotonate is partially

[122] Biginelli, *Ber.*, **24**, 1317 (1891).
[123] Biginelli, *Ber.*, **24**, 2962 (1891).
[124] Biginelli, *Gazz. Chim. Ital.*, **23** (I), 360 (1893); *Ber*, **26**, 447 (1893)
[125] Hinkel and Hey, *Rec. Trav. Chim*, **48**, 1280 (1929).

cleaved to urea and ethyl acetoacetate.[126,127] It was also demonstrated that the Biginelli synthesis is catalyzed by mineral acid, to which the yield is approximately proportional. In the absence of acid, reaction proceeds extremely slowly.

Thiourea can be substituted for urea in this process. With benzaldehyde the thiopyrimidine 92 is formed.[125]
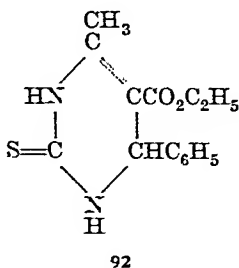
92

α-Amidoalkylation of Active Methylene Compounds Other than Ethyl Acetoacetate with Urea and Aldehydes. Some interesting work using aromatic aldehydes, urea, and β-diketones in acidic media has led to compounds of the type 93.[128,129] Nine aromatic aldehydes were used successfully with pentane-2,4-dione (R = R' = CH₃), and five

93   94
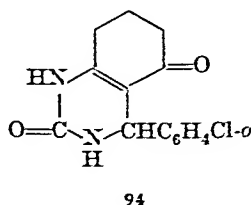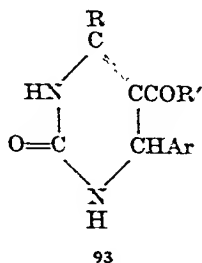
aromatic aldehydes were employed with 1-phenylbutane-1,3-dione. The yields were fair (40–90%), but the positions of the substituents in the butanedione products were not established. Propionaldehyde and urea react with pentane-2,4-dione in an analogous fashion (32% yield), but heptanal and isovaleraldehyde do not.

Cyclohexane-1,3-dione reacts with o-chlorobenzaldehyde and urea to give the bicyclic compound 94 in 80% yield.[130] The reaction is not general.

[126] Folkers, Harwood, and Johnson, J. Am. Chem. Soc., 54, 3751 (1932).
[127] Folkers and Johnson, J. Am. Chem. Soc., 55, 3784 (1933).
[128] Chi and Ling, Acta Chim. Sinica, 22, 177 (1956); Sci. Sinica, 6, 247 (1957) [C.A., 52, 396 (1958)].
[129] Chi and Wu, Acta Chim. Sinica, 22, 184 (1956) [C.A., 52, 6360 (1958)].
[130] Chi and Wu, Acta Chim. Sinica, 22, 188 (1956) [C.A., 52, 6360 (1958)].

n-Butyraldehyde, *p*-methoxybenzaldehyde, and *p*-dimethylaminobenzaldehyde all condensed preferentially with 2 molecules of the diketone to give, after intramolecular dehydration, tricyclic compounds of type 95.

95
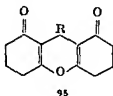
Phenylacetaldehyde did not yield the expected Biginelli product 96. Instead the pyrimidine 97 was obtained.[131] Clearly this arises from the substitution of a molecule of phenylacetaldehyde for the usual ethyl acetoacetate. The same pyrimidine, 97, as expected, was also formed

96   97
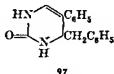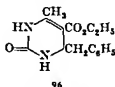
when phenylacetaldehyde and urea were condensed in the absence of acetoacetic ester.

Amidomethylation of Potassium Cyanide with Arenesulfonamidomethanesulfonates. Only one report concerning arenesulfonamidomethanesulfonates seems to have appeared in the literature.[132] The sulfonate 98, prepared by heating *m*-benzenedisulfonamide with sodium hydroxymethanesulfonate, on treatment with excess aqueous

98   99
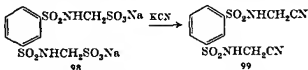
potassium cyanide produced the dinitrile 99 in 75% yield. The nitrile is readily hydrolyzed to the corresponding dicarboxylic acid. The reaction with benzenesulfonamide proceeds in an analogous fashion.

Preparation of the Electrophilic Reagents

If there is any process within the scope of this review which has received adequate attention, it is the reaction of formaldehyde with cyclic and

[131] Folkers and Johnson, *J. Am. Chem. Soc.*, **55**, 3361 (1933).
[132] Knoevenagel and Lebach, *Ber.*, **37**, 4094 (1904).

acyclic mono- and poly-amides.[133]   Studies of this reaction have
involved the labeling of proteins and peptides,[79] the modification
of nylon polymers,[134,135] the preparation of cross-linking agents for
crease-proofing or softening cotton textiles,[136,137] and the development
of waterproofing agents for textile materials.[138–140]   Furthermore the
commercial importance of urea-formaldehyde and urea-acetaldehyde[141]
polymers has stimulated a number of fundamental investigations in this
area.[142–149]

   N-Methylol-amides and -imides.   Amides and imides react
reversibly with formaldehyde in acid, neutral, or basic media.   The

$$\text{RCONH}_2 + \text{CH}_2\text{O} \rightleftharpoons \text{RCONHCH}_2\text{OH}$$
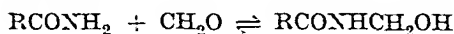
reaction is catalyzed by either acid or base,[143] but, over a relatively wide
pH range (2–12), the activation energy of the reverse reaction remains
greater than that of the forward process by a nearly constant amount
(~ 5 kcal./mole).[144,145,146]   Although the equilibrium favoring the N-
methylolamide is practically unaffected by pH, elevated temperatures
tend to favor the dissociation reaction which has the higher activation
energy.   For this reason the isolation of products often must be carried
out at or near room temperature,[35,84,150] and purifications by recrystal-
lization should be conducted with a minimum of heating.[151,152]   In the
absence of large concentrations of formaldehyde, contact with aqueous
acid or alkali, as expected, causes reversal of the methylolation reaction
even at room temperature.[79]

   Condensation of amides with formaldehyde under neutral or basic
conditions is preferred because acid catalysis often leads to further

[133] Walker, *Formaldehyde*, 2nd ed., Reinhold, New York, 1953, pp. 290–309.

[134] Cairns, Foster, Larchar, Schneider, and Schreiber, *J. Am. Chem. Soc.*, 71, 651 (1949).

[135] Cairns, Gray, Schneider, and Schreiber, *J. Am. Chem. Soc.*, 71, 655 (1949).

[136] Tovey, *Textile Res. J.*, 31, 185 (1961) [*C.A.*, 55, 11859 (1961)].

transformation of the N-methylolamides to the corresponding ethers, $(RCONHCH_2)_2O$, or methylenebisamides, $(RCONH)_2CH_2$. Kinetic studies indicate that the base-catalyzed reactions occur by attack of the amide anion, $RC(=NH)O^{\ominus} \leftrightarrow RC(=O)\overset{\ominus}{N}H$, at the carbonyl carbon atom of formaldehyde.[142,143] This finding explains why reactivity toward formaldehyde under these conditions generally follows the order of increasing amide acidity, e.g.,

$$CH_3CONH_2 < C_6H_5CONH_2 < o\text{-}C_6H_4(CO)_2NH$$
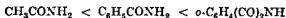
Early work indicated that susceptibility to N-methylolation by formaldehyde was generally restricted to primary amides.[41] The monomethylol derivative of 1,3-dimethylurea[153] and three derivatives of the type $RCON(CH_2OH)_2$,[41,42] were originally the sole exceptions to this rule. Recent work, however, has demonstrated that the reactivity of N-mono-alkylated amides toward formaldehyde is greater than had been supposed.[32,154,154a] Although the reaction may not be complete and products may not be readily isolable in crystalline form, many N-methylol-N-alkylamides can be obtained in good yields as crude oils and can be used in that form.

Unsubstituted[155,156] and N-monosubstituted sulfonamides[157] also react readily with formaldehyde to give the N-methylol derivatives Indications are, however, that they tend to disproportionate to the methylenebisamides and also undergo polymerization more readily than their carboxamide analogs [36]

N-α-Alkylolamides. Most aliphatic and all aromatic aldehydes do not behave toward amides as formaldehyde does. Reaction usually does not stop at the N-alkylol stage, RCONHCHOHR', but progresses further to the alkylidene- or arylidene-bisamide, $(RCONH)_2CHR'$. 1-Ethylol- and 1,3-diethylol-urea have been prepared in crude form from acetaldehyde and urea, but, aside from these, the only exceptions to the rule above are the α-halogenated aldehydes.[141] Chloral, for example, reacts readily with amides, either spontaneously or on heating with or without an acid catalyst, to give the N-alkylolamides, $RCONHCHOHCCl_3$, or "chloralamides".[158] Sulfonamides also react readily.[159] Other aldehydes that

[152] Einhorn and Hamburger, Ann., 361, 122 (1908).
[143] Vail, Moran, and Moore, J. Org Chem , 27, 2067 (1962)
[154a] Chupp and Speziale, J. Org. Chem , 28, 2592 (1963)
[153] Einhorn, Ger. pat. 403,718 (Chem Zentr , 1925, I, 440)
[154] Hug, Bull. Soc. Chim. France, 1934, 990.
[157] Wiedemann and Strassberger, Ger pat. 947,795 [C.A , 53, 2262 (1959)]
[156] Jacobson, Ann., 157, 245 (1871)
[158] Lichtenberger, Fleury, and Barette, Bull. Soc. Chim France, 1955, 669

have been shown to undergo the same condensation are bromal, bromo-dichloroacetaldehyde, dichloroacetaldehyde, dibromoacetaldehyde, and 2,2,3-trichlorobutanal. Numerous examples of these alkylolamides have been reported by Feist[95,160] and by groups led by Chattaway,[161–163] Meldrum,[164–167] and Hirwe.[168–171] Through 1962, however, extension of the reaction to the presently available trifluoroacetaldehyde apparently had not been reported. Also, one might expect some of the recently accessible polyfluorinated ketones to react analogously, especially in view of a recent report showing that carbamyl derivatives of fluorinated aldehydes and ketones are stable.[73] In this instance, however, they were prepared by the action of an alcohol or an amine on an intermediate isocyanate. A number of fluoral carbamates and ureas were prepared in this way.

$$CF_3CHO + HNCO \longrightarrow OCNCHOHCF_3 \xrightarrow{RNH_2} RNHCONHCHOHCF_3$$
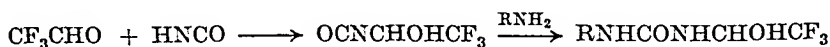
Of incidental interest is another recent report showing that chloral reacts with potassium cyanide or chloral cyanohydrin in aqueous alkali to give a chloral-oxazolidone derivative.[172]
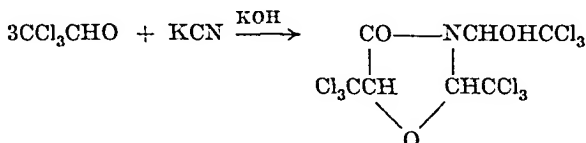
As expected, these N-alkylolamides, like N-methylolamides, are unstable. On being warmed in water or heated above the melting point, they dissociate to amide and aldehyde.[171,173] In alkaline media this occurs at room temperature.[171] Hirwe and Rana have studied the effect

[160] Feist, Ber., 47, 1173 (1914).

[161] Chattaway and James, Proc. Roy. Soc. (London), A134, 372 (1931) [C.A., 26, 1249 (1932)].

[162] Chattaway and James, Proc. Roy. Soc. (London), A137, 481 (1932) [C.A., 26, 5549 (1932)].

[163] Chattaway and James, J. Chem. Soc., 1934, 109.

[164] Meldrum and Bhojraj, J. Indian Chem. Soc., 13, 185 (1936) [C.A., 30, 5940 (1936)].

[165] Meldrum and Tata, J. Univ. Bombay, 6, Pt. II, 120 (1937) [C.A., 32, 3761 (1938)].

[166] Meldrum and Deodhar, J. Indian Chem. Soc., 11, 529 (1934) [C.A., 29, 136 (1935)].

[167] Meldrum and Pandya, J. Univ. Bombay, 6, Pt. II, 114 (1937) [C.A., 32, 3760 (1938)].

[168] Hirwe and Deshpande, Proc. Indian Acad. Sci., 13A, 275 (1941) [C.A., 35, 6250 (1941)].

[169] Hirwe, Gavankar, and Patil, Proc. Indian Acad. Sci., 11A, 512 (1940) [C.A., 34, 7682 (1940)].

[170] Hirwe and Kulkarni, Proc. Indian Acad. Sci., 13A, 49 (1941) [C.A., 35, 5502 (1941)].

[171] Hirwe and Rana, Ber., 72, 1346 (1939).

[172] Bowman, Campbell, and Tanner, J. Chem. Soc., 1963, 692.

[173] Bischoff, Ber., 7, 628 (1874).

of ring substitution on the ease of formation and stability of the N-alkylol-amides, $ArCONHCHOHCCl_3$, derived from chloral and aromatic amides.[171] Some of their findings are unusual and may be of some theoretical interest.

Cyclic N-α-alkylolamides are formed by hydride reduction of certain dicarboxylic imides. α,α-Disubstituted succinimides and glutarimides are reduced by lithium aluminum hydride at the unhindered carbonyl group.[174] Similarly, phthalimides can be reduced selectively with sodium borohydride.[175] Phthalide and o-hydroxymethylbenzamides often appear as by-products, however.
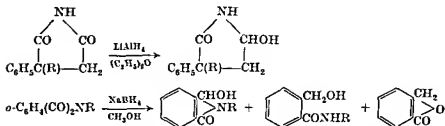
Only one α-alkylolamide appears to have been used directly for the alkylation of a carbon atom.[89] It is 2-hydroxypteridine hydrate (51; see p. 79), prepared by the condensation of 2-hydroxy-4,5-diamino-pyrimidine with glyoxal in aqueous solution.[176] The more common chloralamides have not been employed as α-amidoalkylating reagents. Instead they have been converted to the more reactive halides, $RCONHCHXCX_3$, with which successful alkylation is more likely.

N-Halomethyl- and N-α-Haloalkyl-amides and -imides. A. N-Halomethyl Derivatives. Most N-chloro- or N-bromo-methylamides or -imides have been prepared by treatment of the corresponding N-methylol derivatives with the reagents usually employed for making acid halides from carboxylic acids. Thionyl chloride alone,[177-180] in ether,[181,182] in chloroform,[183] or in benzene[184] provides the most generally convenient reagent for this transformation However, phosphorus pentachloride or

pentabromide alone,[185] in ether,[33,97,99,100,186] in chloroform,[66,187] in a carbon tetrachloride-acetyl chloride mixture,[65] or in dioxane[32,33] have often been used. Phosphorus trichloride or tribromide has also seen occasional service.[8,188,189]

Phosphorus oxychloride has been effective in one instance.[151] Although N-methylolphthalimide on short treatment gave only the symmetrical ether $[o\text{-}C_6H_4(CO)_2NCH_2]_2O$, prolonged heating at reflux temperature converted the ether to N-chloromethylphthalimide. N-Chloromethylphthalimide is also obtainable by warming N-ethoxymethylphthalimide[190] or N-piperidinomethylphthalimide[191] with acetyl chloride.

Certain N-methylolamides can be converted to the halides merely by heating in concentrated hydrochloric or hydrobromic acid.[104,185,192–194] This reaction is not general, for, although N-chloromethylphthalimide can be prepared in this way,[192] N-chloromethylmaleimide cannot.[8] Concentrated sulfuric acid catalyzes the reaction of N-methylolphthalimide with 48% hydrobromic acid.[70,104]

A number of N-chloromethylamides, particularly those derived from fatty acids, have been prepared directly from the amides by treatment with paraformaldehyde and dry hydrogen chloride in an inert solvent such as methylene chloride,[195] benzene,[196–200] dioxane,[201] or glacial acetic acid.[202,203] The products were not isolated but were used directly without

$$RCONH_2 + (CH_2O)_x + HCl \rightarrow RCONHCH_2Cl$$
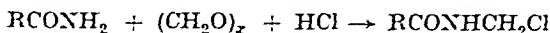
purification. Analyses of the crude mixtures indicated conversions of the order of 20 to 30%. Crude N-chloromethylbenzenesulfonamide, $C_6H_5SO_2NHCH_2Cl$, was also prepared in this way.[201]

Two special methods have been utilized to prepare N-chloro- and N-bromo-methylphthalimides. In one, heating phthalimidoglycyl chloride at 240° effected decarbonylation to the chloromethyl derivative;[192] in the other, N-methylphthalimide with bromine at 160–170° gave the

$$o\text{-}C_6H_4(CO)_2NCH_2COCl \xrightarrow[-CO]{240°} o\text{-}C_6H_4(CO)_2NCH_2Cl$$
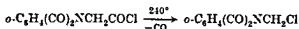
bromomethyl analog reportedly in quantitative yield.[151]

$$o\text{-}C_6H_4(CO)_2NCH_3 \xrightarrow[160°]{Br_2} o\text{-}C_6H_4(CO)_2NCH_2Br$$
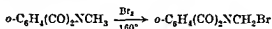
B. N-α-Haloalkyl-amides and -imides. Because the only α-alkylamides that have been isolated in pure form are those derived from α-halogenated aldehydes such as chloral and bromal, most known α-haloalkylamides are derived from them. Almost invariably these have been prepared by warming the alkylolamide with phosphorus pentachloride or pentabromide in the absence of solvent.[106,160,163,204-208]

$$RCONHCHOHCCl_3 \xrightarrow{PBr_3} RCONHCHBrCCl_3 + POBr_3$$
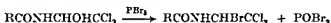
In order to introduce a structural variation in the product, an indirect procedure has been used.[208,209] For example, reduction of the alkylolamide 100 with zinc and acetic acid gave the dichlorovinylamide 101. Either halogen acid (HX) or halogen (X$_2$) can be added to intermediate 101 to give the α-haloalkylamides 102 and 103, respectively.

$$RCONHCHOHCCl_3 \xrightarrow[CH_3CO_2H]{Zn} RCONHCH=CCl_2$$

$$100 \qquad\qquad 101$$

$$\uparrow HX$$

$$RCONHCHXCHCl_2$$
$$102$$

$$\downarrow X_2$$

$$RCONHCHXCXCl_2$$
$$103$$
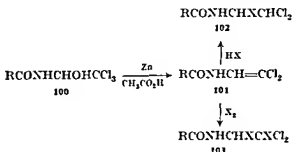
[204] Willard and Hamilton, *J. Am Chem. Soc.*, 75, 2370 (1953)

[205] Howe, Gavankar, and Patil, *Proc. Indian Acad Sci*, 15A, 371 (1941) [*C A*, 36, 1593 (1942)]

[206] Howe and Rana, *J. Indian Chem. Soc.*, 16, 677 (1939) [*C.A*, 34, 473] (1940)]

[207] Yelburgi, *J. Indian Chem. Soc.*, 10, 383 (1933) [*C A*, 28, 466 (1934)].

[208] Yelburgi and Wheeler, *J. Indian Chem Soc*, 11, 217 (1934) [*C A*, 28, 4377 (1934)]

[209] Meldrum and Vad, *J. Indian Chem. Soc*, 13, 117 (1936) [*C A*, 30, 4815 (1936)].

Several N-α-haloalkylphthalimides have been obtained in this way from N-vinyl-[210,211] and N-propenyl-phthalimide.[212,213] For example, addition of dry hydrogen chloride to the former gave a 97% yield of N-α-chloro-ethylphthalimide;[211] and addition of bromine gave the corresponding dibromide, o-$C_6H_4(CO)_2NCHBrCH_2Br$.[210] The latter compound also was

$$o\text{-}C_6H_4(CO)_2NCH{=}CH_2 \xrightarrow{\text{HCl}} o\text{-}C_6H_4(CO)_2NCHClCH_3$$
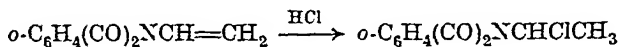
prepared by brominating N-(β-bromoethyl)phthalimide (89% yield) and N-ethylphthalimide (27% yield) with N-bromosuccinimide.[214]

Extension of the decarbonylation reaction mentioned on p. 97 to α-phthalimidobutyric acid produced an α-haloalkyl derivative. When the acid was heated with phosphorus and bromine at 100°, it gave N-(1,3-dibromopropyl)phthalimide in 52% yield.[212,215]

$$o\text{-}C_6H_4(CO)_2NCH(CO_2H)C_2H_5 \xrightarrow[100°]{\text{Br}_2,\text{ P}} o\text{-}C_6H_4(CO)_2NCHBr(CH_2)_2Br$$
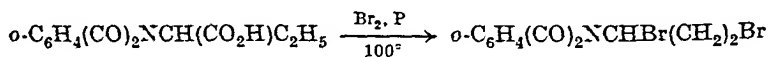
Recent work has shown that acid chlorides will add to imines derived from aromatic aldehydes to give α-chloroalkylamides.[216]

$$ArCH{=}NCH_3 + RCOCl \longrightarrow RCON(CH)_3CHClAr$$
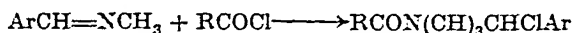
Another recent report describes the preparation of N-(1,2,2,2-tetra-chloroethyl)carbamates by the treatment of the corresponding isocyanate with alcohols and phenols.[73]

$$OCNCHOHCCl_3 \xrightarrow[C_6H_5CH_3,\ 110°]{\text{SOCl}_2} OCNCHClCCl_3 \xrightarrow{\text{ROH}}$$
$$RO_2CNHCHClCCl_3$$
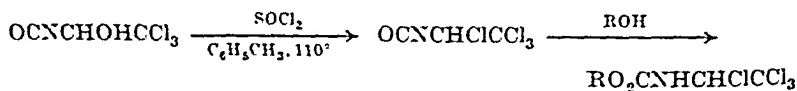
Finally, α-chloroalkyl derivatives of acetamide and of benzenesulfon-amide have been prepared in crude form in solution by direct reaction of the amide, an aldehyde, and dry hydrogen chloride.[201]

$$CH_3CONH_2 + RCHO + HCl \rightarrow CH_3CONHCHClR$$
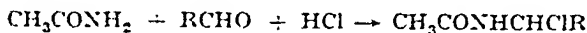
Ethers of N-Methylol- and N-α-Alkylol-amides. *A. Ethers of N-Methylol-amides and -imides.* These substances are most simply prepared by acid-catalyzed alcoholysis of N-methylolamides. Primary alcohols react more readily than secondary,[79] and tertiary carbinols do

$$RCONHCH_2OH \xrightarrow{R'OH,\ H^\oplus} RCONHCH_2OR'$$
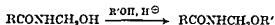
not react at all.[217] Under similar conditions one ether can be made from another by an alkoxyl interchange process.[79,218] With mercaptans thio ethers are formed.[219] Excessive amounts of acid are to be avoided

$$RCONHCH_2OR' \xrightarrow{R''OH,\ H^\oplus} RCONHCH_2OR''$$
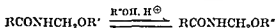
because under such conditions the ethers, like N-methylol compounds, are readily converted to the corresponding methylenebisamides. A pH of about 3 is optimal for stopping the reaction at the ether stage.[217]

In a few instances N-methoxymethyl derivatives of urea have been obtained by direct condensation of formaldehyde with urea in methanol.[149,219] The generality of the method, however, has not been established.

Ethers of less reactive alcohols can be prepared by solvolysis of N-halomethyl-amides or -imides. Thus N-bromomethylphthalimide with triphenylcarbinol gives a 50% yield of the ether.[71]

$$o\text{-}C_6H_4(CO)_2NCH_2OC(C_6H_5)_3.$$

Tertiary carbinols that undergo facile acid-catalyzed elimination, i.e., *t*-butyl alcohol, obviously cannot be etherified in this way.

The tendency for N-methylolamides to undergo self-etherification, i.e.,

$$2RCONHCH_2OH \xrightarrow{-H_2O} (RCONHCH_2)_2O$$
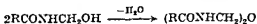
varies with the structure of the amide, but etherification usually can be effected in the presence of controlled amounts of mineral acid (see above). The great ease with which ether formation occurred in some reactions, even in alkaline solutions, led Einhorn to assign to the ethers the isomeric N-methylol-N,N'-methylenebisamide structure.[10,153]

$$RCONHCH_2N(CH_2OH)COR$$
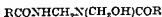
[217] Brace and Mantell, *J. Org. Chem.*, **26**, 5176 (1961).

[218] Zigeuner and Hoselmann, *Monatsh Chem.*, **83**, 5 (1957).

[219] Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936) [*C.A.*, **30**, 5944 (1936)]

On the basis of chemical evidence, however, Zigeuner preferred the symmetrical ether structure.[54] Furthermore, the infrared spectra of a series of derivatives of this type prepared from long-chain alkyl amides showed no hydroxyl absorption,[217] and both the infrared and proton magnetic resonance spectra of the benzamide derivative first reported by Einhorn and co-workers[10] are consistent only for the structure $(C_6H_5CONHCH_2)_2O$.[14] Hence it must be concluded that Einhorn's original structural assignment[10,153] is in error and should be corrected along with several more recent erroneous assignments.[220-222]

2-Tetrahydropyranyloxymethyl isocyanate has been used recently to prepare ethers of N-methylolcarbamates and of N-methylolureas.[73]
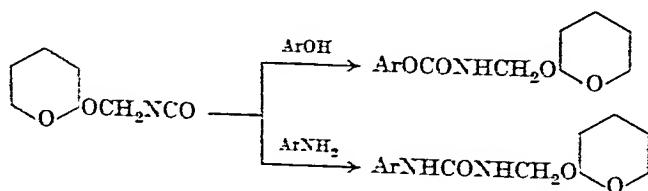
Once formed, most ethers are stable except to hydrolytic conditions. In hot aqueous solution or in cold 1N alkali they break down to amide, formaldehyde, and alcohol only slightly less rapidly than do the corresponding N-methylol derivatives.[79]

B. Ethers of N-α-Alkylolamides. Because nearly all N-α-alkylolamides are necessarily restricted to derivatives of chloral and bromal (see pp. 93–94), most of the known ethers likewise fall into the general type

$$RCONHCH(OR')CX_3$$
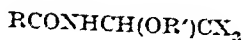
However, among a wide variety of examples the amides used include aliphatic, aromatic, and heterocyclic amides, a lactam, imides, carbamates, and urea derivatives.

Three methods used for the preparation of the N-methylol ethers may also be used for the synthesis of ethers of N-α-alkylolamides. They are acid-catalyzed alcoholysis of the corresponding N-α-alkylol derivative.[223] alcoholysis of the N-α-haloalkyl compound,[106,204,205,214] and direct reaction

of an amide derivative with an aldehyde in an acidic alcoholic medium.[224]

$$
\begin{array}{l}
\text{ROCONHCHOH} \xrightarrow{\text{R'OH, H}^\oplus} \text{ROCONHCHOR'} \\
\text{ROCONHCHOH} \qquad\qquad \text{ROCONHCHOR'} \\
\text{RCON(R')CHXR'} \xrightarrow{\text{R''OH}} \text{RCON(R')CH(OR'')R'}
\end{array}
$$

$$
\begin{array}{ccc}
\begin{array}{c}\text{CH}_2\text{NH}\\|\\\text{CO}\\|\\\text{CH}_2\text{NH}\end{array}
\xrightarrow[\text{ROH, HCl}]{\text{CH}_2\text{CHO}}
\begin{array}{c}\text{CH}_2\text{NCH(OR)CH}_3\\|\\\text{CO}\\|\\\text{CH}_2\text{NH}\end{array}
\xrightarrow{}
\begin{array}{c}\text{CH}_2\text{NCH(OR)CH}_3\\|\\\text{CO}\\|\\\text{CH}_2\text{NCH(OR)CH}_3\end{array}
\end{array}
$$
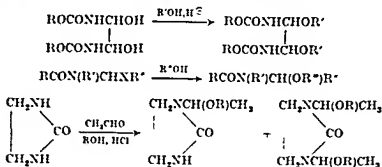
In addition, alkylation with dimethyl sulfate has been employed to prepare a number of methyl ethers.[161 166 208 225,226]

$$
\text{RCONHCHOHR'} \xrightarrow[\text{Aq NaOH}]{\text{(CH}_3\text{)}_2\text{O}_4} \text{RCONHCH(OCH}_3\text{)R'}
$$
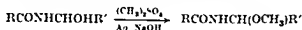
A base-catalyzed ether interchange process has been utilized in several instances.[161-163] The symmetrical ether employed as the starting material is readily obtainable from the N-α-alkylol derivative by using

$$
[\text{RNHCONHCH(CX}_3\text{)}]_2\text{O} \xrightarrow[\text{R OH}]{\text{NaOR}} 2\text{RNHCONHCH(OR')CX}_3
$$
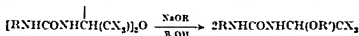
an acid anhydride or an acid chloride under Schotten-Baumann conditions (refs. 94, 95, 160, 161, 163, 166, 168, 207, 208, 226-229). Workers who first encountered this reaction believed that simple elimination had

$$
2\text{RCONHCHOHCX}_3 \xrightarrow[\text{Aq NaOH}]{\text{(CH}_3\text{CO)}_2\text{O}} [\text{RCONHCH(CX}_3\text{)}]_2\text{O}
$$
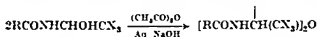
occurred to produce N-acylimines of type RCON=CHCX$_3$.[94 229 230] It remained for Feist to recognize the bimolecular nature of the dehydration and to assign the correct structure to the symmetrical ethers.[95] In acid media the dehydration reaction is largely prevented, and normal esterification of the hydroxyl group predominates (see below). In this connection it is known that certain N-acetyl ketimines spontaneously add

[224] Yost, U.S. pat. 2,550,208 [*C.A.*, **54**, 569 (1960)].
[225] Hurwe and Gavankar, *J. Univ. Bombay*, **6**, II, 123 (1937) [*C A* , **32**, 3762 (1938)].
[226] Hurwe and Rana, *J. Univ. Bombay*, **7**, Pt. 3, 174 (1938) [*C A.*, **33**, 3779 (1939)].
[227] Chattaway, Kerr, and Lawrence, *J. Chem Soc* , 1933, 30
[228] Hurwe and Patil, *Proc. Indian Acad. Sci.*, **13A**, 273 (1941) [*C.A.*, **35**, 6250 (1941)].
[229] Moscheles, *Ber.*, **24**, 1803 (1891).
[230] Hantzsch, *Ber.*, **27**, 1248 (1894).

alcohols to give ethers.   In contrast, the analogous N-benzoyl ketimines
do so with comparative reluctance.[231]

$$CH_3CON{=}CAr_2 + ROH \xrightarrow{\text{(Fast)}} CH_3CONHC(OR)Ar_2$$

$$C_6H_5CON{=}CAr_2 + ROH \xrightarrow{\text{(Slow)}} C_6H_5CONHC(OR)Ar_2$$
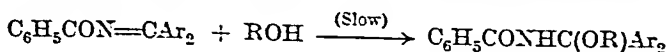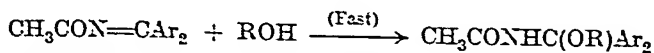
A special method has been applied to the preparation of N-α-alkoxyethyl
derivatives of imides and of one sulfonamide: reaction with vinyl ethers
at elevated temperatures.[232]   In the presence of acid, however, the
products derived from imides eliminate the elements of alcohol to give

$$o\text{-}C_6H_4(CO)_2NH + CH_2{=}CHOR \xrightarrow[\text{No acid}]{160{-}260°} o\text{-}C_6H_4(CO)_2NCH(OR)CH_3$$

$$p\text{-}CH_3C_6H_4SO_2NHCH_3 + CH_2{=}CHOR \xrightarrow[\text{Acid}]{60°}$$

$$p\text{-}CH_3C_6H_4SO_2N(CH_3)CH(OR)CH_3$$
$$\text{(84\%)}$$
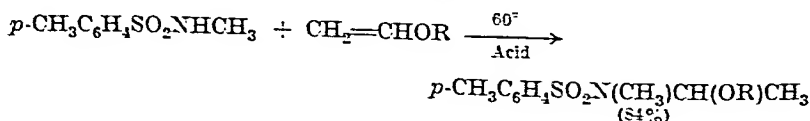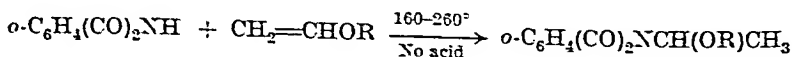
vinyl imides, e.g., $o\text{-}C_6H_4(CO)_2NCH{=}CH_2$.   By contrast, carboxamides
and primary sulfonamides generally react with vinyl ethers (with or
without acid catalysis) to produce N,N'-ethylidenebisamides,

$$(RCONH)_2CHCH_3$$
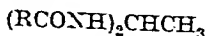
(see below).[232,233]

Another special method for preparing N-α-alkoxyethyl derivatives of
carbamyl compounds consists of the treatment of α-alkoxyethyliso-
cyanates with alcohols or amines.[234]

$$HNCO + ROCH{=}CH_2 \rightarrow$$

$$OCNCH(OR)CH_3 \quad \begin{array}{l} \xrightarrow{R'OH} R'OCONHCH(OR)CH_3 \\ \xrightarrow{R'NH_2} R'NHCONHCH(OR)CH_3 \end{array}$$
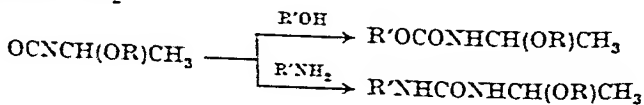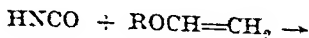
Esters of N-Methylol- and of N-α-Alkylol-amide Derivatives.
A. Esters of N-Methylolamides.   N-Methylolamides readily undergo
acetolysis.[79]   Most esters of N-methylolamides, however, have been
prepared by conventional acylation methods.   These include reaction of

$$RCONHCH_2OH + CH_3CO_2H \xrightarrow[\text{20 min.}]{75°} RCONHCH_2OCOCH_3$$
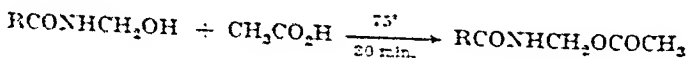
the methylolamide with an acid anhydride alone,[222,235–237] in the presence of catalytic amounts of sulfuric acid[5] or of the corresponding sodium salt;[238–241] treatment with an acid chloride or anhydride in pyridine (refs. 8, 66, 181, 194, 242, 243) or in aqueous alkali;[237,238,241] and heating with a carboxylic acid in the presence of hydrogen chloride[240] or trifluoro-acetic anhydride.[8] The formyl derivative, o-C$_6$H$_4$(CO)$_2$NCH$_2$OCHO, was prepared (24% yield) by heating N-chloromethylphthalimide in formamide at 100°;[220] N-acetoxymethylmaleimide was obtained (43% yield) by acetolysis of N-chloromethylmaleimide at 100°;[8] and the phthalimido-methyl esters of a number of carbobenzoxyamino acids and peptides have been prepared by the treatment of N-chloromethylphthalimide with the amino acid in the presence of triethylamine.[243a]

Esters of N-methylolamides may serve as useful derivatives for isolation and purification. Thus N-methyl-N-methylolacetamide, which could not be obtained in crystalline form, was converted to the acetate CH$_3$CON(CH$_3$)CH$_2$OCOCH$_3$, which could be distilled under reduced pressure.[244]

A direct preparation of esters of N-methylolamides from amides would greatly increase their usefulness as amidomethylating agents. One example of this synthetic simplification is the preparation of N-acetoxymethylstearamide directly from stearamide.[138] The relatively mild conditions used in the procedure suggest that it may be generally applicable to the synthesis of other esters of this type.

B. Esters of N-α-Alkylolamides. Nearly all substances of this type are either acetates or benzoates of chloral- or bromal-amide derivatives, RCONHCH(OCOR')CX$_3$. They have usually been made by direct acylation of the corresponding hydroxy compound with acetyl chloride or benzoyl chloride either alone[94,168] or in the presence of pyridine.[101,166,204] Acetic anhydride with catalytic amounts of concentrated sulfuric acid generally gives the corresponding acetate (refs. 161, 162, 166, 168, 225, 228), but in the presence of aqueous sodium hydroxide it usually produces the symmetrical ether (see p. 101).[94,95,160] This tendency toward ether formation is also governed, however, by the nature of the α-alkylolamide.

[235] Pikl, U.S. pat. 2,477,349 [C.A., 44, 168 (1950)].
[236] Shipp, U.S. pat. 2,222,463 [C.A., 35, 3459 (1941)].
[237] Spurr, *Roczniki Chem.*, 29, 455 (1954) [C.A., 50, 311 (1956)].
[238] Monti and Venturi, *Gazz. Chim. Ital.*, 78, 365 (1948) [C.A., 42, 1261 (1948)].
[239] Zellner, *Austrian pat.* 176,561 [C.A., 48, 10778 (1954)].
[240] Zellner, *Austrian pat.* 176,562 [C.A., 48, 10778 (1954)].
[241] Zellner, *Ger. pat.* 927,269 (*Chem. Zentr.*, 1955, 7980)
[242] Euzhorn and Fribelmann, *Ann.*, 361, 153 (1908).
[243] Muzuch, Kasatkin, and Gelfer, *J. Gen. Chem. USSR* (*Engl. Transl*), 27, 213 (1957).
[243a] Nefkens, *Nature*, 193, 974 (1962), *Rec. Trav. Chim.*, 82, 941 (1963)
[244] Walter, Steffen, and Heyns, *Chem. Ber.*, 94, 2462 (1961).

Thus with acetic anhydride and aqueous sodium hydroxide the chloral-amides 104 give mainly the symmetrical ethers 105. The unmethylated analogs 106, on the other hand, yield the corresponding acetates 107 as the major products.[226]
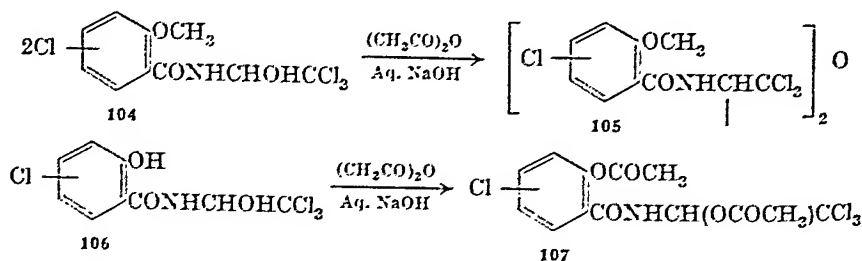
A few esters have been made by acidolysis of the corresponding N-α-chloroalkylamides.[205,211]

$$\text{RCONHCHClR}' \xrightarrow[\text{C}_6\text{H}_5\text{CO}_2\text{H}]{\text{CH}_2\text{CO}_2\text{H or}} \text{RCONHCH(OCOR'')R}'$$
$$(\text{R}''=\text{CH}_3, \text{C}_6\text{H}_5)$$
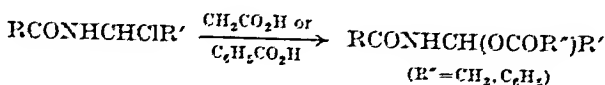
N,N'-Methylenebis-amides and -imides. N,N'-Methylenebisbenz-amide was first prepared in 1876 by the action of methylal on benzonitrile in the presence of concentrated sulfuric acid.[245] Later this so-called

$$\text{C}_6\text{H}_5\text{CN} + \text{CH}_2(\text{OCH}_3)_2 \xrightarrow[\text{H}_2\text{SO}_4]{\text{Concd.}} (\text{C}_6\text{H}_5\text{CONH})_2\text{CH}_2$$
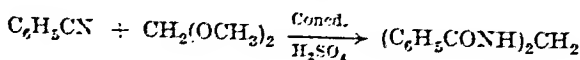
"Hipparaffin" was obtained more readily by heating benzamide with formalin in acid solution.[246] Since then this method has become one of general utility, having been applied to many simple amides, some N-

$$2\text{C}_6\text{H}_5\text{CONH}_2 + \text{CH}_2\text{O} \xrightarrow{\text{H}^{\ominus}} (\text{C}_6\text{H}_5\text{CONH})_2\text{CH}_2$$
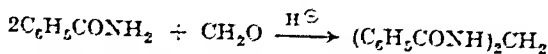
monosubstituted amides,[247–249] acyclic[55,153,250,251] and cyclic[155,252] carbamyl compounds, and a few aromatic sulfonamides.[25,156] Although mineral acid is most often used as the catalyst, other conditions successfully employed have included heating the components alone or in acetic anhydride or glacial acetic acid, or even warming in the presence of weak

aqueous base (dilute potassium carbonate solution). The ubiquity of this reaction is readily understood from the fact that N,N'-methylenebisamides usually represent the end products (and most stable ones) derived from the reaction of amides with formaldehyde in acid media. Thus N,N'-methylenebisamides are obtainable by acid treatment of both N-methylolamides and symmetrical ethers as well as of unsymmetrical ethers and esters of N-methylolamides.

$$RCONH_2 \xrightarrow{CH_2O} RCONHCH_2OH
\begin{array}{l}
\xrightarrow[H^{\ominus},\ -H_2O]{RCONH_2} (RCONH)_2CH_2 \\[1em]
\xrightarrow[H^{\ominus},\ -H_2O]{RCONHCH_2OH} (RCONHCH_2)_2O
\end{array}
$$

with $(RCONH)_2CH_2 \xrightarrow{H^{\ominus},\ -CH_2O}$
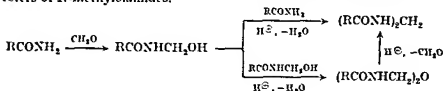
An interesting specificity in catalytic requirement for one of these reactions has been observed recently[253] Heating N-methylol-2,3-dibromoisobutyramide with aqueous hydrobromic or sulfuric acid gave the corresponding bisamide, but identical treatment with aqueous hydrochloric acid did not. Furthermore, the same transformation could be effected in the presence of bromine but not with iodine.[253,254]

$$2CH_2BrC(CH_3)BrCONHCH_2OH \xrightarrow[H_2SO_4]{HBr\ or} [CH_2BrC(CH_3)BrCONH]_2CH_2$$
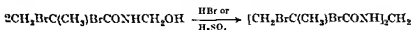
Perhaps the most general method and the one giving the best yields involves treatment of an amide with an N-methylolamide in acid solution. It has the added advantage of flexibility in that unsymmetrical bisamides are obtainable in this way These unsymmetrical derivatives can be

$$RCONH_2 + R'CONHCH_2OH \xrightarrow{H^{\oplus}} RCONHCH_2NHCOR'$$
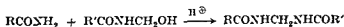
prepared also by treatment of nitriles with N-methylolamides in strong sulfuric acid. Thus acetonitrile and N-methylolphthalimide in concentrated sulfuric acid give N-acetylaminomethylphthalimide in 93% yield.[84]

$$o\text{-}C_6H_4(CO)_2NCH_2OH + CH_3CN \xrightarrow[H_2SO_4]{Concd} o\text{-}C_6H_4(CO)_2NCH_2NHCOCH_3$$
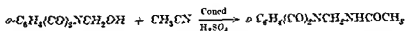
Under these conditions nitriles react more readily with N-methylolamides than they do with formaldehyde. A study designed to test this generalization showed that in a formic-sulfuric acid solution at 30° a mixture of

[253] Feuer and Bello, *J. Am. Chem. Soc.*, 78, 4367 (1956).

[254] Feuer and Lynch, *J. Am. Chem. Soc.*, 75, 5027 (1953).

p-chlorobenzonitrile, formaldehyde, and N-methylolbenzamide gave almost exclusively the unsymmetrical bisamide (reaction a).[255]

$$p\text{-ClC}_6\text{H}_4\text{CONHCH}_2\text{NHCOC}_6\text{H}_5 \xleftarrow[(a)]{\text{C}_6\text{H}_5\text{CONHCH}_2\text{OH}} p\text{-ClC}_6\text{H}_4\text{CN} \xrightarrow[(b)]{\text{CH}_2\text{O}} (p\text{-ClC}_6\text{H}_4\text{CONH})_2\text{CH}_2$$
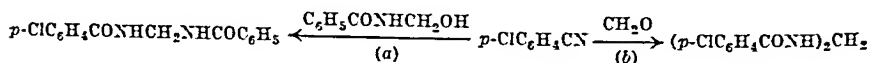
A few special methods have been employed for making certain methylenebis-amides and -imides. N,N'-Methylenebisphthalimide has been prepared by treating potassium phthalimide with methylene iodide[256] or, preferably (48% yield), with the methiodide of N-dimethylaminomethylphthalimide.[81] Similarly, chloromethylamides[178,194] and aminomethylamides[82,257] have been used to amidomethylate imides and sulfonamides

$$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NK} + o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\overset{\oplus}{\text{N}}(\text{CH}_3)_3 \text{ I}^{\ominus} \rightarrow [o\text{-C}_6\text{H}_4(\text{CO})_2\text{N}]_2\text{CH}_2$$
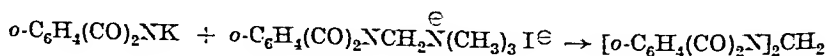
or their alkali metal salts.

A recently reported method for preparing N,N'-methylenebisurethans appears to be general.[258] An example is the reaction of methylal with two equivalents of methyl isocyanate to give dimethyl N,N'-dimethyl-N,N'-methylenebiscarbamate. Thioformals react analogously to give

$$\text{CH}_2(\text{OCH}_3)_2 + 2\text{CH}_3\text{NCO} \rightarrow \text{CH}_2[\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_3]_2$$
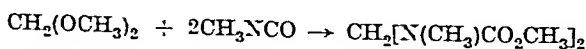
methylenebisthiocarbamates. By another apparently general process, unsymmetrical combinations of amides with urethan have been obtained through the Curtius reaction of N-acylglycylhydrazides.[157,259]

$$\text{CH}_2\text{ClCONHCH}_2\text{CONHNH}_2 \xrightarrow{\text{HNO}_2}$$

$$[\text{CH}_2\text{ClCONHCH}_2\text{CON}_3] \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \text{CH}_2\text{ClCONHCH}_2\text{NHCO}_2\text{C}_2\text{H}_5$$
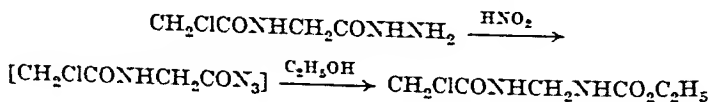
Finally, acetylation of the Mannich-type products derived from some anilines and an oxazolidinethione has given several unsymmetrical bisamides.[260]
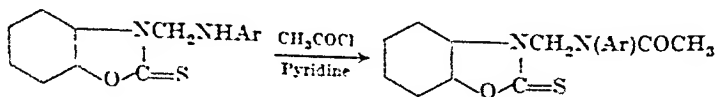
N,N'-Methylenebisamides generally are stable crystalline solids. N,N'-Methylenebisbenzamide can be sublimed,[215] and N,N'-methylenebis-phenylacetamide can be distilled.[261] Compounds of this type usually are stable in 1N sodium hydroxide at 90°,[79] but treatment with hot dilute mineral acid reconverts them to the corresponding amides. As expected, hot concentrated acid or hot alcoholic alkali hydrolyzes them to the carboxylic acids.[245,261] Of some interest is the report that methylene-diamine can be prepared in solution by hydrolysis of N,N'-methylenebis-formamide with cold concentrated mineral acid.[262] Einhorn had previously reported similar results from the alkaline hydrolysis of N,N'-methylenebistrichloroacetamide.[263,264]

$$CH_2(NHCHO)_2 \xrightarrow{H^{\oplus}} [CH_2(NH_2)_2] \xleftarrow{OH^{\ominus}} CH_2(NHCOCCl_3)_2$$
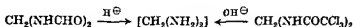
Treatment of methylenebisurea with dilute hydrochloric acid leads to polymeric products of the type $H_2NCONH(CH_2NHCONH)_nH$.[219,265]

N,N'-Alkylidene- and -Arylidene-bisamides. The first example of this type, diethyl N,N'-dichloroethylidenebiscarbamate, was prepared in 1840 by the action of chlorine on an ethanolic solution of hydrocyanic acid.[266] Its structure, however, was not determined until thirty years

$$Cl_2 + C_2H_5OH + HCN \rightarrow (C_2H_5OCONH)_2CHCHCl_2$$

$$CHCl_2CHO + 2H_2NCO_2C_2H_5 \xrightarrow{-H_2O}$$
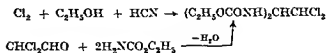
later, when it was obtained by the reaction of dichloroacetaldehyde with urethan.[173,267] The latter method has been the basis for the preparation of several hundred compounds of this class. Synthetic variations include heating the components together without solvent,[268-270] in ethanol,[271,272]

[241] Hepp, Ber., 10, 1649 (1877).

[242] Knudsen, Ber., 47, 2698 (1914).

[243] Einhorn, Ann., 343, 207 (1905).

[244] Einhorn and Mauermayer, Ann., 343, 305 (1905).

[245] Staudinger and Wagner, Makromol. Chem., 12, 168 (1954) [C. A., 49, 12302 (1955)].

[246] Stenhouse, Ann., 33, 92 (1840).

[247] Bischoff, Ber., 5, 80 (1872).

[248] Bojanović, Vandjel, Mihailović, and Stefanović, Ber. Chem. Ges. Belgrade, 20, 267 (1955) [Chem. Zentr., 1957, 6712].

[249] Ittyerah and Pandya, Proc. Indian Acad. Sci., 15A, 258 (1942) [C.A., 37, 2725 (1943)].

[270] Schiff, Ann., 148, 330 (1868).

[271] Nigam and Pandya, Proc. Indian Acad. Sci., 29A, 56 (1949) [C.A., 43, 8182 (1949)].

[272] Schiff, Ann., 151, 186 (1869).

water,[123,272] pyridine,[273-276] aqueous acid,[173,277,278] glacial acetic acid,[154,279] or acetic anhydride.[250-252] The last method appears to be the most generally useful. However, condensation in refluxing benzene with azeotropic removal of water has also met with moderate success.[253]

Most of the commonly available primary amides and carbamyl compounds have been utilized in reactions with aldehydes. Even a few N-monosubstituted amides have been included.[270,276] By heating benzaldehyde and 2-furaldehyde with mixtures of two different amides, mixed N,N'-benzylidene- and N,N'-furylidene-bisamides have been obtained in yields ranging from 25 to 42%.[254]

$$ArCHO + RCONH_2 + R'CONH_2 \rightarrow RCONHCH(Ar)NHCOR'$$

Diamides with suitably positioned functional groups yield cyclic bisamides. Oxamide and malonamide derivatives lead to diketotetrahydroimidazoles[255] and diketohexahydropyrimidines,[256] respectively.

$$(CONH_2)_2 + C_6H_5CHO \rightarrow \begin{array}{c} CONH \\ | \quad \diagdown \\ \quad \quad CHC_6H_5 \\ | \quad \diagup \\ CONH \end{array}$$

$$(C_2H_5)_2C(CONH_2)_2 + C_6H_5CHO \rightarrow (C_2H_5)_2C \begin{array}{c} CONH \\ \diagup \quad \diagdown \\ \quad \quad CHC_6H_5 \\ \diagdown \quad \diagup \\ CONH \end{array}$$
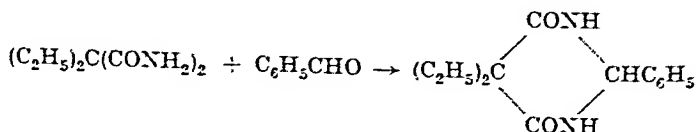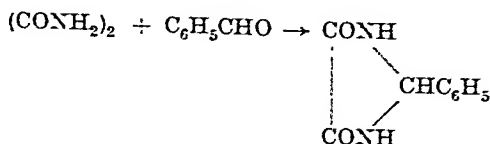
aldehydes. One reason is the occurrence of a side reaction in which tetra-substituted pyrazines are formed.[271,257]

$$4ArCHO + 2HCONH_2 \rightarrow \text{[pyrazine structure with Ar groups]}$$
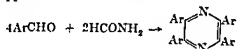
Phthalimide does not react with benzaldehyde even in the presence of acetic anhydride.[85] This behavior is consistent with the fact that hydantoins undergo *acid-catalyzed* condensation with acetals (and with formaldehyde[185,252,258,289]) preferentially at the amide nitrogen atom.[290]

$$CH_2ClCH(OC_2H_5)_2 + 2 \text{[structure]} \xrightarrow[H_2SO_4]{CH_2CO_2H} \text{[product structure]}$$
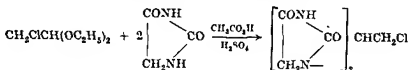
In interesting contrast is the demonstration that in *neutral* solution formaldehyde reacts at the imide nitrogen atom to give the 3-methylol derivative.[187] This alteration in reaction course is consistent with the

$$\text{[structure]} + CH_2O \xrightarrow{Neutral} \text{[product structure]}$$
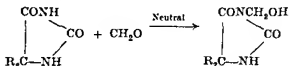
idea that the acid-catalyzed process involves attack at the more nucleophilic (amide) nitrogen atom by a protonated aldehyde species,[290] while the reaction in neutral solution occurs through attack of the neutral aldehyde by the anion derived from the more acidic (imide) nitrogen atom

Sulfonamides, likewise, do not react readily with aldehydes to give bisamides. Ethylidenebis-(p-toluenesulfonamide), however, has been obtained (11% yield) from the acid-catalyzed reaction of p-toluenesulfonamide with phenyl vinyl ether.[232] This appears to be a general method for preparing the corresponding biscarboxamides as well.[232,233]

$$2 \, p\text{-}CH_3C_6H_4SO_2NH_2 + CH_2=CHOC_6H_5 \xrightarrow{H^\oplus} (p\text{-}CH_3C_6H_4SO_2NH)_2CHCH_3 + C_6H_5OH$$
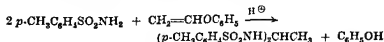
Simple ketones, unlike aldehydes, do not react with amides. Perfluorinated ketones, however, might be expected to behave like aldehydes and

[281] Bülow, *Ber.*, **26**, 1972 (1893).
[288] Rogers, U.S. pat. 2,404,096 [*C.A.*, **40**, 6096 (1946)]
[289] Walker, U.S. pat. 2,417,999 [*C.A.*, **41**, 4511 (1947)]
[290] Johnson and Crosby, *J. Org. Chem.*, **27**, 2077 (1962).

give bisamides, provided that the reaction does not stop at the α-alkylol stage, as it usually does with perhalogenated aldehydes, i.e., chloral. This supposition gains support from the fact that both pyruvic acid[291] and benzoylformic acid[292] give bisamides with acetamide. The pyruvic acid

$$RCOCO_2H + CH_3CONH_2 \xrightarrow[-H_2O]{Heat} (CH_3CONH)_2C(R)CO_2H$$
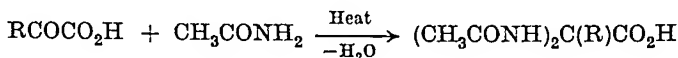
derivative loses one acetamide residue in hot glacial acetic acid, and α-acetamidoacrylic acid is formed.[292–294]

$$(CH_3CONH)_2C(CH_3)CO_2H \longrightarrow$$
$$CH_3CONHC(CO_2H){=}CH_2 + CH_3CONH_2$$
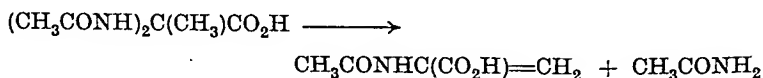
If proper conditions are employed, even chloral and its analogs yield bisamides rather than the usual α-alkylol compounds. The conditions include the use of concentrated sulfuric acid as the condensing agent either with a nitrile[4,245,261,295] or with an amide.[296] However, a possible side

$$CCl_3CHO + 2RCN + H_2O \xrightarrow[H_2SO_4]{Concd.} (RCONH)_2CHCCl_3$$
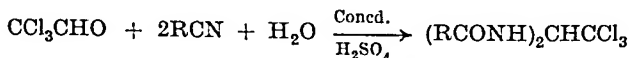
reaction in this and similar condensations of aromatic aldehydes with carboxamides and sulfonamides must be anticipated. When a Lewis acid is used as a catalyst in the condensation of a sulfonamide with an aromatic aldehyde, an arylidenemonoamide (or sulfonylimine) is produced.[159]

$$RSO_2NH_2 + ArCHO \xrightarrow[ZnCl_2]{Heat} RSO_2N{=}CHAr$$
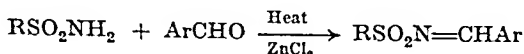
Of some interest is the observation that the three hydroxybenzaldehydes react with amides to give the acylimines, ArCH=NCOR, under the same conditions that lead to bisamides, ArCH(NHCOR)$_2$, from the corresponding methoxybenzaldehydes.[296a,297–299] Similarly, 5-chloro- and 3,5-dichloro-salicylaldehyde, when heated with heptanamide, benzamide, or benzene-sulfonamide, give only the acylimine (or sulfonylimine) derivatives even though no Lewis acid is present.[271] However, these are exceptional cases.

[291] Bergmann and Grafe, Z. Physiol. Chem., 187, 187 (1930).
[292] Shemin and Herbst, J. Am. Chem. Soc., 60, 1954 (1938).
[293] Süs, Ann., 569, 153 (1950).
[294] Wieland, Ohnacker, and Ziegler, Chem. Ber., 90, 194 (1957).
[295] Hubner, Ber., 6, 109 (1873).
[296] Batt and Woodcock, J. Chem. Soc., 1948, 2322.
[296a] Mehra and Pandya, Proc. Indian Acad. Sci., 10A, 285 (1939) [C.A., 34, 1981 (1940)].
[297] Manzur and Pandya, Proc. Indian Acad. Sci., 10A, 282 (1939) [C.A., 34, 1980 (1940)].
[298] Mehra and Pandya, Proc. Indian Acad. Sci., 10A, 279 (1939) [C.A., 34, 1980 (1940)].
[299] Pandya and Sodhi, Proc. Indian Acad. Sci., 7A, 361 (1938) [C.A., 32, 7434 (1938)].

As a rule, alkylidene- and arylidene-bisamides resemble the methylenebis-amides in their high thermal stability and in their behavior toward acids and bases.

N-Aminomethylamides and Their Quaternary Salts. The voluminous literature dealing with N-aminomethylamides has been reviewed recently.[3] No purpose would be served by repeating this information here. It should suffice to note that three related methods have been used to synthesize these compounds: a Mannich-type reaction of amides with formaldehyde and amines,[79,257,300-302] reaction of amines with N-methylolamides,[79,65,303] and reaction of amides with N-methylol-amines or N,N'-methylenediamines.[303] The first method is, by far, the

$$RCONH_2 + CH_2O + R_2'NH$$
$$RCONHCH_2OH + R_2'NH \big\} \longrightarrow RCONHCH_2NR_2'$$
$$RCONH_2 + HOCH_2NR_2'$$
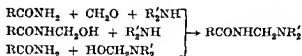
most convenient and, consequently, the most commonly used.

Three types of quaternary salts of N-aminomethylamides are known. The first is prepared by alkylation of the tertiary amine with methyl or ethyl iodide.[1,179,180,194,304] The second is obtained by treating pyridine

$$RCONHCH_2NR_2' + R'I \rightarrow RCONHCH_2\overset{\oplus}{N}R_2'R'I^{\ominus}$$
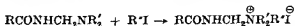
with an N-chloromethylamide (pure[66] or prepared *in situ*[199,200,305]), or by reaction of pyridine hydrochloride in pyridine ether with a preformed N-methylolamide[140,235,243] or with an amide and formaldehyde.[138,306]
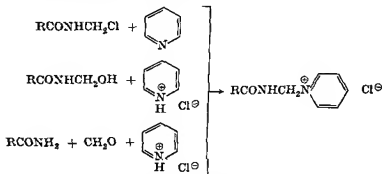
[300] Bohme, Dietz, and Leidreiter, *Arch. Pharm.*, **287**, 198 (1954).
[301] Einhorn, Ger. pat. 281,440 [*Chem. Zentr.*, **1915**, II, 108).
[302] Feldman and Wagner, *J. Org Chem.*, **7**, 31 (1942).
[303] Weaver, Simons, and Baldwin, *J. Am. Chem. Soc.*, **66**, 222 (1944).
[304] Hellmann and Loschmann, *Chem Ber.*, **87**, 1684 (1954).
[305] Hunt and Bradley, U.S. pat. £.493,068 [*C A ·*, **44**, 3041 (1950)).
[306] Baldwin, Evans, and Salkeld, U.S. pat. 2,278,417 [*C A ·*, **36**, 5032 (1942)]

The third results when an aminomethylamide is heated with an acid halide.[191]

$$RCONHCH_2NR_2' + R''COX \rightarrow (RCONHCH_2)\overset{\ominus}{N}R_2'X^{\ominus} + R''CONR_2'$$
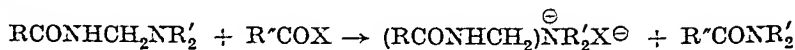
N-Acyl- and N-Sulfonyl-imines. Consideration of compounds of this type will be restricted to derivatives of aldehydes and ketones lacking an α-hydrogen atom. When an α-hydrogen atom is present, tautomerization to the corresponding enamide becomes possible (see pp. 115–116).

As stated previously, reactions of amides with aromatic aldehydes generally lead to N,N'-arylidenebisamides. A number of hydroxybenzaldehyde derivatives are exceptions to this rule and give acylimines instead.[271,297-299] These have been noted on p. 110.

Several other amide-aldehyde combinations also react anomalously. These are chloroacetamide with chloral and bromal,[307] urethan with glyoxal,[308] and thiourea with chloral.[160] For the last combination, reaction occurs normally at one nitrogen atom to give the chloralurea derivative, but abnormally at the other to give the acylimine structure.

$$CH_2ClCONH_2 + CX_3CHO \xrightarrow{100°} CH_2ClCON{=}CHCX_3$$

$$C_2H_5OCONH_2 + (CHO)_2 \xrightarrow{H^{\ominus}} (C_2H_5OCON{=}CH)_2$$

$$CS(NH_2)_2 + 2CCl_3CHO \longrightarrow CS\begin{smallmatrix} \nearrow N{=}CHCCl_3 \\ \\ \searrow NHCHOHCCl_3 \end{smallmatrix}$$
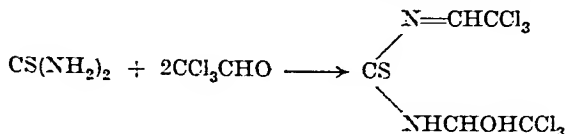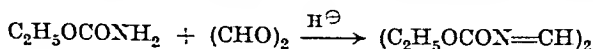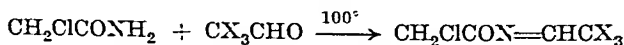
Bis-trichloroethylideneurea has been prepared by the elimination of 2 moles of acetic acid from the diacetate of chloralurea.[160]

$$CO[NHCH(OCOCH_3)CCl_3]_2 \xrightarrow{HCl, heat} CO(N{=}CHCCl_3)_2 \cdot HCl$$
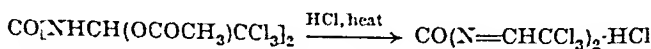
Although sulfonamides react with chloral to give the corresponding N-α-alkylolamides, they condense with aromatic aldehydes to the N-sulfonylimines.[159] Zinc chloride is used as a catalyst. Interestingly, sulfonylimines are also obtained from the reaction of 2-furamide with arenesulfonyl chlorides in pyridine solution.[159]

$$RSO_2NH_2 + ArCHO \xrightarrow{ZnCl_2} RSO_2N{=}CHAr$$
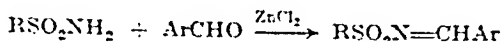
N-Acyl derivatives of aromatic ketimines can be prepared by acylation of the isolated imine.[231] It is usually more convenient, however, to acylate the intermediate halomagnesium derivative obtained by the action of an aromatic Grignard reagent on an aromatic nitrile.[19,120,231]

$$RCOCl + Ar_2C{=}NH \rightarrow RCON{=}CAr_2$$

$$ArCN + Ar'MgX \longrightarrow [Ar(Ar')C{=}NMgX] \xrightarrow{RCOCl} RCON{=}C(Ar)Ar'$$
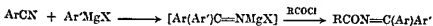
Amidomethanesulfonic Acids and Their Sodium Salts. Few compounds of this type have been reported since Knoevenagel and Lebach first made them in 1904 by heating carboxamides or sulfonamides with aqueous sodium formaldehyde bisulfite under pressure.[132] The only

$$RSO_2NH_2 + HOCH_2OSO_2Na \xrightarrow[H_2O]{200°} RSO_2NHCH_2SO_3Na$$
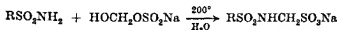
sulfonic *acid* of this class was prepared by the reaction of N-bromomethyl-phthalimide with aqueous sodium sulfite[309]

$$o\text{-}C_6H_4(CO)_2NCH_2Br + Na_2SO_3 \rightarrow o\text{-}C_6H_4(CO)_2NCH_2SO_3H$$
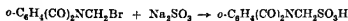
Related Compounds of Potential Utility as Electrophilic Reagents

Many compounds not yet employed as α-amidoalkylating agents bear a sufficient structural resemblance to those that have been so employed to suggest that the former might react analogously to the latter under suitable conditions. In the compilation that follows, an attempt has been made, mainly on the basis of structural analogy, to place the more likely candidates ahead of the less likely ones. For this reason the cyclic analogs, which might be expected to be most stable and least reactive, have been placed last.

Amidomethyl Thio Ethers and Thiol Esters. *A. From N-Methylol-amides and Mercaptans*[79,219,310,311] *or Thiourea.*[312,313]

$$RCONHCH_2OH + R'SH \xrightarrow{H^{\ominus}} RCONHCH_2SR'$$

$$RCONHCH_2OH + CS(NH_2)_2 \xrightarrow{HCl} RCONHCH_2SC({=}NH)NH_2 \cdot HCl$$
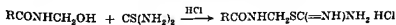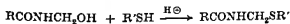
[309] Balaban, *J. Chem. Soc.*, **1926**, 569
[310] Benson and Cairns, *J. Am. Chem. Soc.*, 70, 2115 (1948).
[311] Monti and Franchi, *Gazz. Chim. Ital.*, 85, 510 (1955) [*C.A.*, 50, 4932 (1956)].
[312] Albrecht, Frei, and Sallmann, *Helv. Chim. Acta*, 24, 233E (1941).
[313] Société pour l'Industrie Chimique à Bâle, Fr. pat. 849,147 [*C.A.*, 35, 6357 (1941)].

B. From N-Halomethyl-amides[190,195,314] or -imides[190,315] and Mercaptans[190,315] or Thiourea.[195,314]

$$o\text{-}C_6H_4(CO)_2NCH_2X + RSH \xrightarrow{(-HX)} o\text{-}C_6H_4(CO)_2NCH_2SR$$

$$RCONHCH_2Cl + CS(NH_2)_2 \longrightarrow RCONHCH_2SC(=NH)NH_2\cdot HCl$$
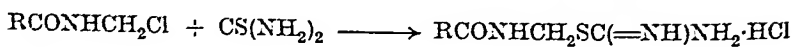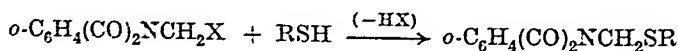
C. From N-Halomethyl-amides[198] or -imides[8,104,316,317] or Carbamyl Compounds[178-180,218] and Alkali Metal Mercaptides,[178-180] Thiocyanates,[8,104,193] Xanthates,[317] Dithiocarbamates,[317] or Dithiophosphates.[316]

$$o\text{-}C_6H_4(CO)_2NCH_2X + \overset{\ominus\ominus}{MSY} \to o\text{-}C_6H_4(CO)_2NCH_2SY$$

$$[X = Cl, Br; M = \overset{\ominus}{Na}, K^{\ominus}; Y = CN, -C(=S)OR, -C(=S)NR_2, -P(=S)(OR)_2]$$
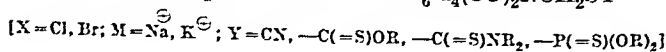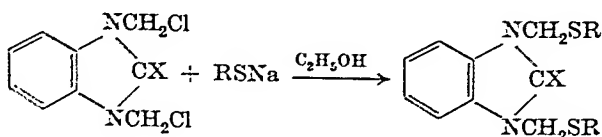
D. From Dialkylaminomethylamides and Mercaptans.[319]

$$RCONHCH_2NR_2' + R''SH \xrightarrow[NaOH]{C_6H_5CH_3} RCONHCH_2SR'' + R_2'NH$$

$$(R' = CH_2, C_2H_5; R = alkyl, aryl)$$
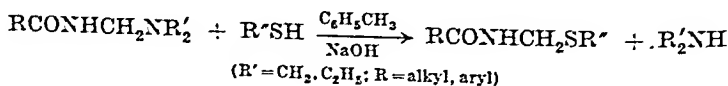
E. From Amides, Aldehydes, and Thiolacetic Acid.[220]

$$RCONH_2 + ArCHO + CH_3COSH \xrightarrow{H^{\ominus}} RCONHCH(Ar)SCOCH_3$$

$$(R = CH_3, C_2H_5O; Ar = aryl)$$
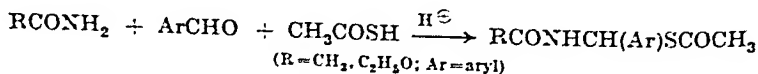
F. From Formamide and an Aminomethyl Sulfide.[220]

$$HCONH_2 + (C_2H_5)_2NCH_2SC_6H_4CH_3\text{-}p \xrightarrow{150°}$$

$$HCONHCH_2SC_6H_4CH_3\text{-}p + (C_2H_5)_2NH$$
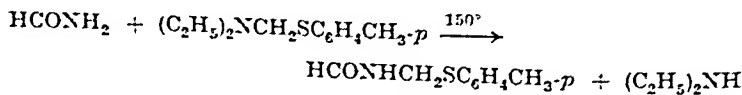
G. From Methyl Isocyanate and Thioformals.[258]

$$2CH_3NCO + CH_2(SC_4H_9\text{-}n)_2 \to n\text{-}C_4H_9SCON(CH_3)CH_2SC_4H_9\text{-}n$$
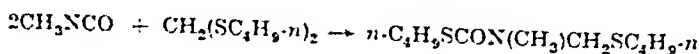
A. By Reduction of Chloral- or Bromal-amides.[207-209]

$$RCONHCHOHCX_3 \xrightarrow[CH_3CO_2H]{Zn} RCONHCH{=}CX_2$$

(R = alkyl, aryl; X = Cl, Br)
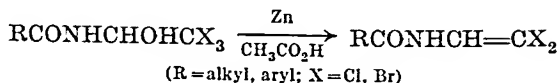
B. By Dehydration of Dihaloacetalamides.[208]

$$ArCONHCHOHCHCl_2 \xrightarrow[\text{or } (CH_3CO)_2O-H_2SO_4]{P_2O_5,\ heat} ArCONHCH{=}CCl_2$$
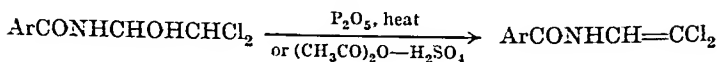
C. From Amides and α-Keto Acids[291-294] *or Diarylacetaldehydes.*[324a]

$$RCONH_2 + R_2'CHCOCO_2H \longrightarrow$$

$$\begin{bmatrix} RCONHC(OH)(CHR_2')CO_2H \\ or \\ (RCONH)_2C(CHR_2')CO_2H \end{bmatrix} \xrightarrow[(-RCONH_2)]{(-H_2O)\ or} RCONHC(CO_2H){=}CR_2'$$

(R = alkyl, aryl, R' = H, alkyl, aryl)

$$RCONHR' + Ar_2CHCHO \rightarrow RCON(R')CH{=}CAr_2$$

(R = alkyl, aryl, alkoxy, amino; R' = H, CH_3; Ar = aryl)
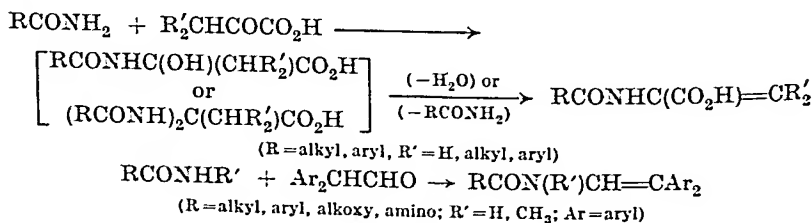
D. From the Methyl Ester of N,O-Diformyl-DL-serine.[325]

$$HCONHCH(CO_2CH_3)CH_2OCHO \xrightarrow{150°} HCONHC(CO_2CH_3){=}CH_2$$
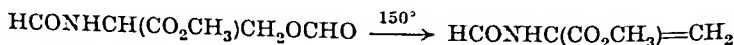
E. By Vinylation of Amides.[326]

$$RCONHR' + HC{\equiv}CH \xrightarrow[\text{Heat, pressure}]{KOH} RCON(R')CH{=}CH_2$$
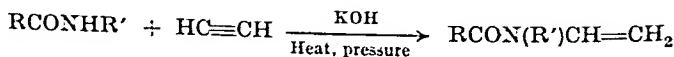
F. By Vinylation of Imides.[232]

$$X(CO)_2NH + CH_2{=}CHOR \xrightarrow[\text{Acid}]{\text{Heat}} X(CO)_2NCH{=}CH_2$$

[X(CO)_2NH = succinimide, phthalimide]
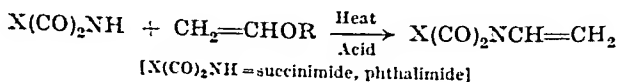
G. From Hydantoins and Aldehydes.[327]

(X = O, S; R = aryl, alkyl)
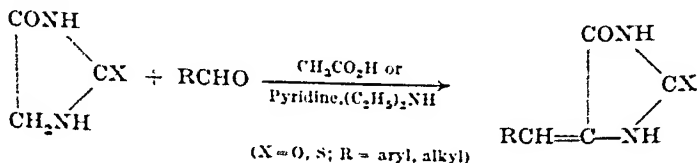
[324a] Eiden and Nagar, *Arch. Pharm.*, **296**, 415 (1963).

[325] Heyns and Heinecke, *Z. Physiol. Chem.*, **331**, 45 (1963).

[326] Reppe, *Neue Entwicklungen auf dem Gebiet der Chemie des Acetylens und Kohlenoxyds.* Springer-Verlag, 1949, pp. 20–21; Copenhaver and Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold, 1949, pp. 66–67.

[327] Ware, *Chem. Rev.*, **46**, 431–433 (1950).

5-Hydroxyhydantoins. *A. Alloxanic Acid Derivatives from Alloxan.*[9,328]
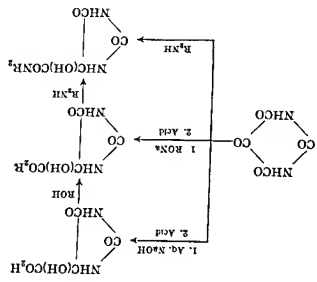
B. 5-Hydroxyhydantoins from Alloxanic Acid and 1,3-Dimethylparabanic Acid.[329]

$$(R = CH_3, COC_6H_5, CONHC_6H_5)$$
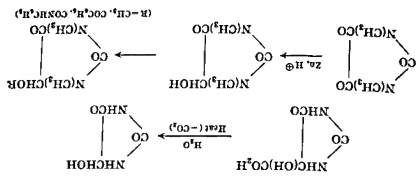
Glycol Amides, Carbamates, and Ureas, and Derived Products. *A. From Glyoxal and Amides or Carbamates.*[223,330]

$$2RCONH_2 + (CHO)_2 \xrightarrow[\text{}]{H_2O} (RCONHCHOH)_2 \xrightarrow[H^\ominus]{R\,OH} (RCONHCHOR')_2$$

$$(R = \text{alkyl, alkoxyl})$$
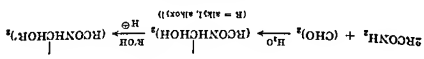
[328] Faber and Day, *J. Am. Chem. Soc.*, 77, 4894 (1955).

[329] Biltz and Kobel, *Ber.*, 54, 1802 (1921); Biltz and Heinrich, *ibid.*, 54, 1329 (1921).

[330] Badische Anilin and Soda-Fabrik A.-G., Fr. pat. 1,129,263 (*Chem. Zentr.*, 1958, 1603).

B. From Glyoxal and Diamides.[331]

$$\begin{array}{c}\text{NHCOR} \\ (CH_2)_n \\ \text{NHCOR}\end{array} \;+\; (CHO)_2 \xrightarrow{H_2O} \begin{array}{c}\text{COR} \\ | \\ \text{N}-\text{CHOH} \\ (CH_2)_n \\ | \\ \text{N}-\text{CHOH} \\ | \\ \text{COR}\end{array}$$

$$(n=1, 2;\; R=H,\, CH_3)$$
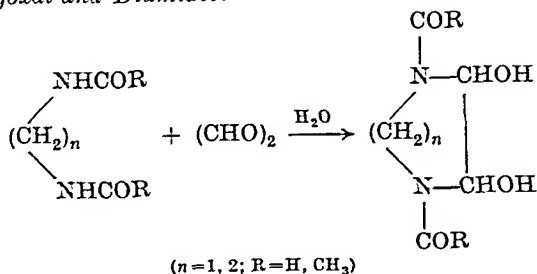
C. From Glyoxal and Ureas.[223,308,332–335]

$$CO(NHR)_2 \;+\; (CHO)_2 \xrightarrow{H_2O} CO \begin{array}{c} \text{N(R)CHOH} \\ | \\ \\ \text{N(R)CHOH}\end{array} \xrightarrow[H^{\ominus}]{R'OH} CO \begin{array}{c}\text{N(R)CHOR'} \\ | \\ \\ \text{N(R)CHOR'}\end{array}$$

$$(R=H,\, CH_3,\, CH_2OH)$$
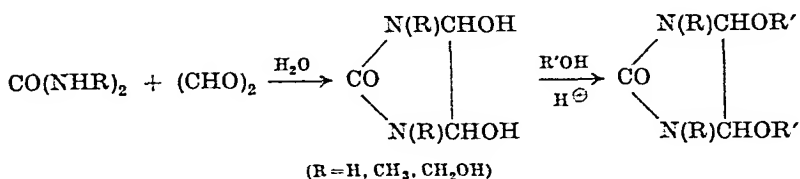
D. From Diketosuccinic Esters and Urea.[336]

$$CO(NH_2)_2 \;+\; (COCO_2R)_2 \xrightarrow{CH_3CO_2H} CO\begin{array}{c}\text{NHC(OH)CO}_2\text{R} \\ | \\ \\ \text{NHC(OH)CO}_2\text{R}\end{array}$$

ROH / H$^{\ominus}$ CH$_3$COCl   NH$_3$

$$CO\begin{array}{c}\text{NHC(OR)CO}_2\text{R} \\ | \\ \\ \text{NHC(OR)CO}_2\text{R}\end{array} \qquad CO\begin{array}{c}\text{NHC(OCOCH}_3\text{)CO}_2\text{R} \\ | \\ \\ \text{NHC(OCOCH}_3\text{)CO}_2\text{R}\end{array} \qquad CO\begin{array}{c}\text{NHC(OH)CONH}_2 \\ | \\ \\ \text{NHC(OH)CONH}_2\end{array}$$

$$(R=CH_3,\, C_2H_5)$$
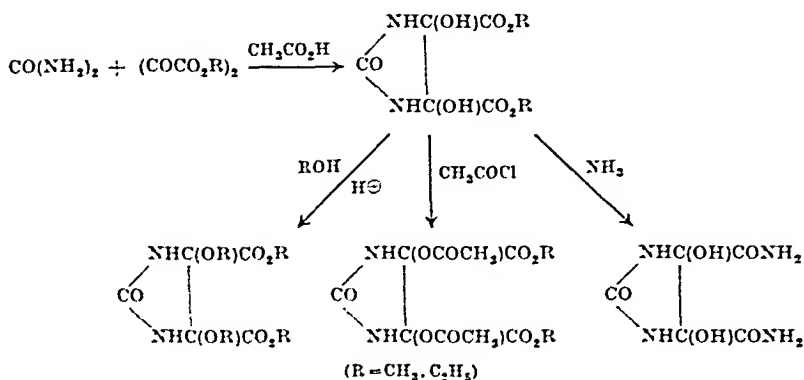
[331] Vail, Moran, Moore, and Kullman, *J. Org. Chem.*, **27**, 2071 (1962).

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[335] Vail, Murphy, Frick, and Reid, *Am. Dyestuff Reptr.*, **50**, 27 (1961) [*C.A.*, **55**, 19254 (1961)].

[336] Geisenheimer and Anschütz, *Ann.*, **306**, 35 (1899).

E. From 4,5-Diaryl-2-imidazolones.[337–343]

$(R=H, CH_3, C_2H_5; R'=CH_3, C_6H_5; Ar=C_6H_5, p\text{-}BrC_6H_4, p\text{-}CH_3OC_6H_4; X=Cl, Br)$
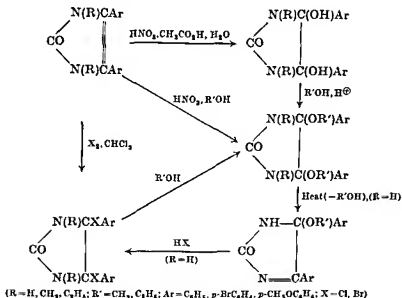
Cyclic Esters and Carbamates of N-α-Alkylolamides. A. N-Acyl- and N-arenesulfonyl-5-oxazolidinones.[344–347]

$$R(X)NHCH(R')CO_2H + CH_2O \xrightarrow[C_6H_6(-H_2O)]{H^{\oplus}} R(X)N\text{---}CHR'$$

$(R=alk)l, aryl, R'=H, alk)l, X=CO, SO_2)$
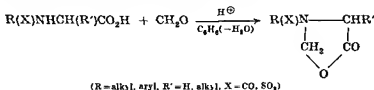
B. 2-Trichloromethyl-4,5-oxazolidinedione [160]

$$C_2H_5OCOCONHCHOHCCl_3 \xrightarrow[2.\quad H^{\oplus}]{1. \text{ Aq } Na_2CO_3} NHCHCCl_3$$
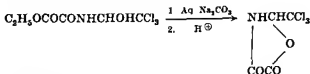
[337] Biltz, Ber., 41, 167, 1754, 1761 (1908).
[338] Biltz, Ann., 368, 262 (1909).
[339] Biltz and Behrens, Ber., 43, 1990 (1910).
[340] Biltz and Kosegarten, Ann., 368, 219, 228, 236 (1909).
[341] Biltz and Krebs, Ann., 363, 218 (1909).
[342] Biltz and Rumpel, Ann., 365, 173, 201, 206 (1909)
[343] Dunnavant, J. Org Chem., 21, 1513 (1956).
[344] Ben-Ishai, J. Am. Chem. Soc., 79, 5736 (1957).
[345] Chemische Fabrik auf Aktien, Ger. pat. 148,669 (Chem. Zentr., 1904, I, 411).
[346] Chemische Fabrik auf Aktien, Ger pat 153,860 (Chem. Zentr., 1904, II, 678).
[347] Micheel and Thomas, Chem. Ber., 90, 2906 (1957).

C. ε-Phthalimido-ε-caprolactone.[348]

$$o\text{-}C_6H_4(CO)_2N\text{-cyclohexanone} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{CF}_3\text{CO}_3\text{H}} o\text{-}C_6H_4(CO)_2N\text{-lactone}=O$$

(43%)
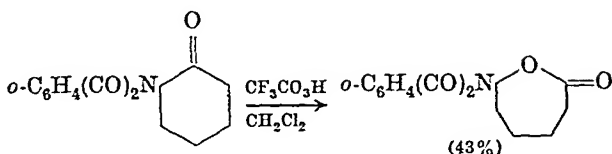
D. 1,3,5-Oxadiazine-2,4-diones.[73]

$$OCNC(OH)RR' \xrightarrow{\text{H}_2\text{O}} \text{ring}$$

(R = R' = CF$_3$ or CF$_2$Cl and R = H, R' = CCl$_3$)
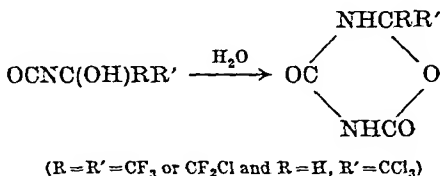
Cyclic Ethers and Thio Ethers of N-α-Alkylolamides. A. 4-Oxazolidinones and 4-Thiazolidinones.[349–351]

$$RCH(XH)CONH_2 + R'COR'' \xrightarrow[(-\text{H}_2\text{O})]{\text{H}^{\ominus}} \text{ring}$$

(R, R', R'' = H, CH$_3$, C$_6$H$_5$; X = O, S)
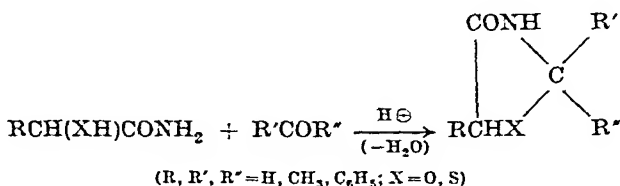
B. N-Sulfonyloxazolidines.[352]

$$RSO_2NHCH_2CH(R')OH + R''CHO \xrightarrow[\text{C}_6\text{H}_6(-\text{H}_2\text{O})]{\text{H}^{\ominus}} \text{ring}$$

(R, R' = H, CH$_2$OH; R'' = alkyl, aryl)
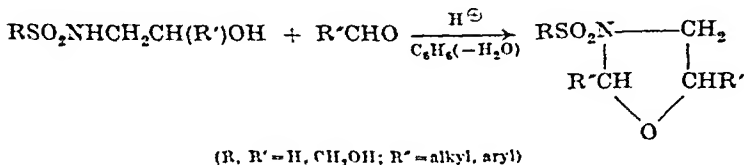
[348] Smissman and Bergen, J. Org. Chem., 27, 2316 (1962).
[349] Davies, Ramsey, and Stove, J. Chem. Soc., 1949, 2633.
[350] Fischer, Danzschat, and Stettiner, Ber., 65, 1032 (1932).
[351] Michaël and Jeanprêtre, Ber., 25, 1678 (1892).
[352] Raitz, U.S. pat. 2,722,531 [C.A., 50, 3503 (1956)].

C. N-(2-Tetrahydropyranyl)amides.[353-355]

(R = alkyl, aryl; X = CO, SO₂)
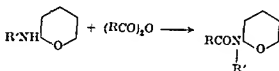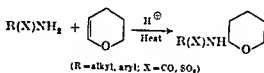
D. N-[2,3-Dihydropyranyl-(2)]-carbamates and -carbamides.[356]

(R = O-alkyl, NH-alk); R' = H CH₃)
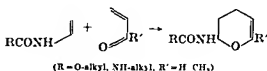
E. Urons.[357]
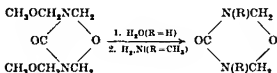
F. Diacyltetrahydro-1,3,5-oxadiazines[305]

(R = alkyl)
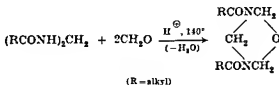
[353] Glacet and Troude, *Compt. rend.*, **253**, 681 (1961).
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[355] Speziale, Ratts, and Marco, *J. Org. Chem.*, **26**, 4311 (1961).
[356] Schulz and Hartmann, *Chem. Ber.*, **95**, 2733 (1962).
[357] Beachem, Oppelt, Cowen, Schuckedantz, and Maier, *J. Org. Chem.*, **28**, 1876 (1963)

G. 2,3-Dihydro-1,3-benzoxazin-4-ones.[166,278,350,358-374]

$$(X=H, Cl, Br, acyl; R=alkyl, aryl; R'=H, alkyl)$$
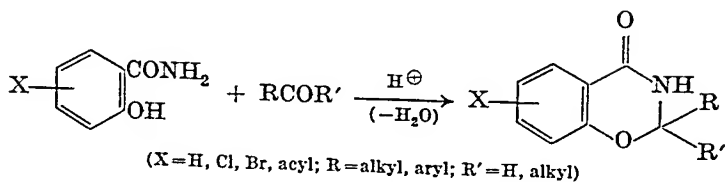
H. 2,3-Dihydro-1,3-benzthiazin-4-ones.[358,375-377]

$$(R=alkyl, aryl; R'=H, alkyl)$$
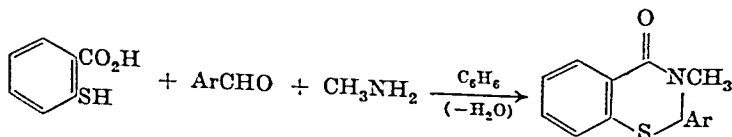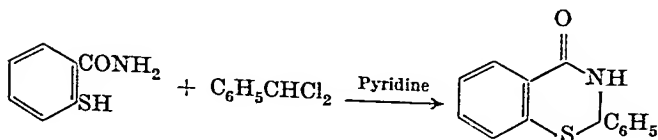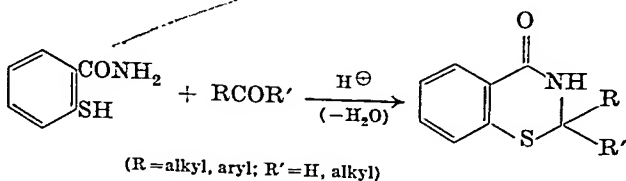
[358] Böhme and Boeing, *Arch. Pharm.*, **294**, 556 (1961).

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[369] Ohnacker, Ger. pat. 1,021,848 [*C.A.*, **54**, 4633 (1960)].

[370] Ohnacker and Scheffler, Ger. pat. 1,063,169 [*C.A.*, **55**, 12432 (1961)].

[371] Ohnacker and Scheffler, U.S. pat. 2,943,087 [*C.A.*, **54**, 24818 (1960)].

[372] Rana, *J. Indian Chem. Soc.*, **19**, 299 (1942) [*C.A.*, **37**, 2361 (1943)].

[373] Titherley, *J. Chem. Soc.*, **91**, 1419 (1907).

[374] Titherley and Hicks, *J. Chem. Soc.*, **95**, 908 (1909); Titherley and Hughes, *ibid.*, **97**, 1368 (1910).

[375] Böhme and Schmidt, *Arch. Pharm.*, **286**, 330 (1953).

[376] Boudet, *Bull. Soc. Chim. France*, **1955**, 1518.

[377] Loev, *J. Org. Chem.*, **28**, 2160 (1963).

CHOICE OF EXPERIMENTAL CONDITIONS

It is difficult to make generalizations about optimum conditions for carrying out the numerous reactions included in this review. Impressions in this regard are best derived from the specific discussions of the foregoing section. A few general remarks can be made at this point, however.

Choice of Reactants

If the end product sought from an amidoalkylation reaction is the amine, an amidoalkylation reagent with an easily removable acyl group is to be preferred. This is especially important when the reaction product may not resist treatment with the strong acid or base often necessary for acyl cleavage. Thus the phthalimido group of p-phthalimidomethylphenol could not be removed, either by the hydrazine method or by hydrolytic means[15] without destroying the molecule. Similarly no way was found to hydrolyze derivatives of the type $ArCH(C_6H_5)NHCOR$ ($Ar = $ hydroxyaryl; $R = CH_3$ or C_6H_5) to the corresponding amines.[74] Consistent with these results is the observation that the ease of acid hydrolysis of amides of the type $ArCH_2NHCOR$ ($Ar = $ hydroxyaryl) decreased in the order $R = H$, C_6H_5, CH_3, CH_2Cl, C_6H_5, and that the formamide derivative was especially easily hydrolyzed.[75]

To obtain the best yield of monosubstitution product from a relatively reactive substrate it is often desirable to select an amidoalkylating agent of minimal reactivity. Excessive reactivity generally leads to polysubstitution and consequent reduction in yield of the desired product.

When attempts were made to amidomethylate relatively unreactive substrates with N-methylolamides under acid-catalyzed conditions, methylenebisamides, $(RCONH)_2CH_2$, were often encountered as by-products,[20,47] and sometimes as the only products. (N-Methylolbenzamide is especially prone to disproportionation in this way.) This result is an indication that the use of a more electrophilic reagent, e.g., N-methylolphthalimide, may be in order or that more strongly acidic conditions might be employed to force the reaction in the desired direction.

Choice of Conditions

In most reactions, monosubstitution is favored by increasing the ratio of substrate to reagent. In a few favorable instances either mono- or di-substitution can be effected at will, each to the virtual exclusion of the other, merely by using the reactants in the proper stoichiometric ratio. Thus equivalent quantities of p-toluidine and N-methylolphthalimide in

concentrated sulfuric acid gave the monosubstitution product **108** in 81% yield,[44] whereas two equivalents of the phthalimide reagent gave the
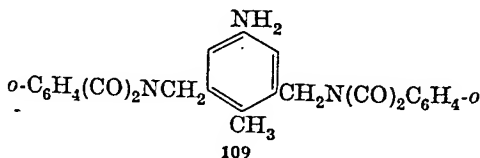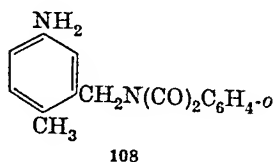
disubstituted derivative **109** in 95% yield under the same conditions.[29]

Even the concentrations of reactants can be varied to affect the yield. For example, in the reaction of o-chlorobenzoic acid with N-methylolchloroacetamide to give the product **110**, the 65% yield obtained was reduced to 40% when the quantity of sulfuric acid was halved.[57] The
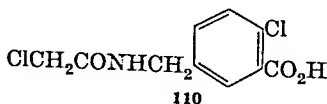
generality of this effect of concentration on yield has not been established, but it should be regarded as a potentially important variable.

EXPERIMENTAL PROCEDURES

α-Amidoalkylation of Aromatic Carbon Atoms

N-(2-Hydroxy-3,5-dinitrobenzyl)phthalimide from 2,4-Dinitrophenol and N-Methylolphthalimide in 5% Oleum.[69] An intimate mixture of 9 g. (0.049 mole) of 2,4-dinitrophenol and 9 g. (0.051 mole) of N-methylolphthalimide is gradually added to 35 g. of 5% fuming sulfuric acid cooled in ice. After the mixture has stood at room temperature for 10 minutes with occasional stirring, it is warmed slowly and finally heated for 40 minutes on the steam bath. The cooled reaction mixture is then poured in a thin stream into 200 ml. of vigorously stirred ethanol, and the resulting mixture is boiled for 1–2 minutes. After it has cooled, the precipitate is collected and recrystallized from nitrobenzene or glacial acetic acid to give 16.8 g. (95%) of the N-arylmethylphthalimide, m.p. 210–211°.

2-Chloro-5-(chloroacetylaminomethyl)benzoic Acid from 2-Chlorobenzoic Acid and N-Methylolchloroacetamide in Concentrated Sulfuric Acid.[57] A mixture of 277.8 g. (1.76 moles) of 2-chlorobenzoic acid and 700 ml. of concentrated sulfuric acid is stirred

and cooled to 20°. Powdered N-methylolchloroacetamide (202 g., 1.8 moles) is added over a 30-minute period while the temperature is maintained at 20°. The reaction mixture is stirred overnight, and the solution is poured over ice and allowed to stand for 2 days. The solid is collected, washed with water, dried, and triturated with diethyl ether. The solid (m.p. 126–135°) is again recrystallized from ethanol to give 300 g. (65%) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid, m.p. 144–146°. Recrystallization from dioxane and then from dimethylformamide raises the melting point to 147–148°.

N-Benzyl-N-methylacetamide from Benzene and N-Methyl-N-methylolacetamide with Boron Trifluoride.[32] Through a stirred suspension of 20.6 g. (0.2 mole) of N-methyl-N-methylolacetamide in 100 ml. of dry benzene is passed a slow stream of boron trifluoride while the temperature is maintained at 60° by means of a cold water bath. When the mixture is saturated and no more heat is evolved, it is cooled in an ice bath, then poured into ice water and separated. The aqueous phase is extracted with diethyl ether, and the combined benzene and ether layers are dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate leaves an oil which is fractionally distilled to give 22.0 g. (68%) of N-benzyl-N-methylacetamide, b.p. 91–93°/0.2 mm., m.p. 40–41°.

N-(2'-Methyl-5'-nitrobenzyl)-2-pyrrolidinone from 4-Nitrotoluene, 2-Pyrrolidinone, and Paraformaldehyde in Concentrated Sulfuric Acid.[34] To 600 ml. of concentrated sulfuric acid maintained at 20° are added with stirring 274 g. (2.0 moles) of 4-nitrotoluene, 60 g. (2.0 moles) of paraformaldehyde, and 170 g. (2.0 moles) of 2-pyrrolidinone. The solution is allowed to stand at room temperature for 12–15 hours, then at 45° for 6 hours, and finally at 65° for 12 hours. It is then cooled and poured over ice, and the oily product is washed with water by decantation until free of acid. The washed oil is taken up in a minimum amount of warm carbon tetrachloride. The white crystals which deposit on cooling are collected and dried. There is obtained 174 g. (37%) of N-(2'-methyl-5'-nitrobenzyl)-2-pyrrolidinone, m.p. 94–96°

N,N'-Diacetyl-4,6-di(aminomethyl)-1,3-xylene from m-Xylene, Acetonitrile, and Formaldehyde in 85% Phosphoric Acid.[5] In a 5-l. three-necked flask fitted with a Hershberg stirrer, condenser, and thermometer are placed 1.5 l. of 85% phosphoric acid, 360 g. (11 moles) of 91% paraformaldehyde, 530 g. (5.0 moles) of m-xylene, and 535 g. (13 moles) of acetonitrile. The mixture is heated with vigorous agitation to 65° whereupon a spontaneous reaction occurs. The temperature is held at 65–75° until the exothermic reaction is over, and then at 90° for 4 hours. After cooling there remains a layer of 124–135 g. of unchanged

xylene. The viscous acid layer is added in a slow stream with vigorous agitation to 8 l. of ice water containing 3 l. of concentrated ammonium hydroxide. The resulting suspension is stirred overnight, filtered, and the solid washed with dilute ammonium hydroxide and dried at 75° for 24 hours. The yield of crude diamide, m.p. 225–235°, is 600–611 g. (61–66% based on xylene converted). Recrystallization from methanol gives pure N,N'-diacetyl-4,6-di-(aminomethyl)-1,3-xylene, m.p. 245–246°.

N-(2-Hydroxy-3,5-dimethylbenzyl)-N'-phenylurea from 2,4-Xylenol and the Ether (C₆H₅NHCONHCH₂)₂O, in Formic Acid.[54] A solution of 0.9 g. of 2,4-xylenol and 0.7 g. of the ether in 20 ml. of formic acid is warmed at 50° for 2 hours, poured into water, and allowed to stand for 4 hours. The product is collected and dried. The yield is 90%. Recrystallization from benzene gives the pure diarylurea, m.p. 169°.

N-Benzylphthalimide from Benzene, N-Bromomethylphthalimide, and Zinc Chloride.[14] A solution of 24 g. (0.1 mole) of N-bromomethylphthalimide in 50 ml. of dry benzene is treated with 1 g. of anhydrous zinc chloride and then heated under reflux for 2 hours or until the evolution of hydrogen bromide nearly ceases. The cooled red solution is poured into water, separated, and washed to neutrality with aqueous sodium bicarbonate and water. The organic layer is filtered to remove any insoluble material, and the filtrate is then concentrated. The residual solid (22.6 g., 94%, m.p. 110–113°) is recrystallized once from 100 ml. of ethanol to give 20.2 g. of N-benzylphthalimide, m.p. 113–114°.

2- and 4-Methoxybenzylamine from Anisole and N-Chloromethylphthalimide (Zinc Chloride Catalyst).[378] A mixture of 280 g. (2.9 moles) of anisole, 215 g. (1.1 moles) of N-chloromethylphthalimide, and 11 g. of anhydrous zinc chloride is heated for 2 hours at 120–140°. The excess anisole is removed by steam distillation, and the layer of water is decanted from the pasty residue which crystallizes after trituration with a little ethanol.

The mixture of N-(2- and 4-methoxybenzyl)phthalimide is collected and hydrolyzed directly by stirring it for 2–3 hours at room temperature with a mixture of 250 ml. of ethanol and 1.5 l. of 12% aqueous sodium hydroxide. The mixture is then concentrated under reduced pressure to two-thirds of its original volume and treated carefully with 700 ml. of concentrated hydrochloric acid. After the mixture has been heated on the steam bath for several hours, it is cooled, filtered to remove insoluble material, and the filtrate is concentrated to dryness. The residue is made alkaline with 35% sodium hydroxide solution, and the base which is released is taken up in benzene and dried over anhydrous potassium carbonate. Filtration, removal of the benzene, and distillation of the

378 Shirakawa and Kawasaki, J. Pharm. Soc. Japan, 71, 1213 (1951) [C.A., 46, 5044 (1952)].

residue under reduced pressure give a crude base, b.p. 120–140°/21 mm. Redistillation at atmospheric pressure gives 98 g. (65%) of a mixture of 2- and 4-methoxybenzylamine, b.p. 231–235°.

The mixture of amines is then added dropwise with stirring to 330 g. of 10% anhydrous ethanolic hydrogen chloride. After it has stood overnight at room temperature, the solid is collected, washed with 100 ml. of ethanol, and dried to give 73 g. (38%) of 4-methoxybenzylamine hydrochloride, m.p. 223–230°. Recrystallization from ethanol raises the melting point to 231–233°.

The alcoholic filtrate is concentrated to dryness under reduced pressure to give crude 2-methoxybenzylamine hydrochloride corresponding to a 19% yield based on the original N-chloromethylphthalimide. The crude product can be purified by solution in water and treatment with a hot aqueous solution of picric acid. The 2-methoxybenzylamine picrate, m.p. 227–228°, which is formed can be reconverted through the base, b.p. 120–122°/16 mm., to pure 2-methoxybenzylamine hydrochloride, m.p. 148–149° (from ethanol).

4-Phthalimidomethyl-1-naphthol-8-sulfonic Acid γ-Sultone from 1,8-Naphthsultone and N-Chloromethylphthalimide with Aluminum Chloride.[379] A stirred mixture of 62 g. (0.3 mole) of 1,8-naphthsultone, 71 g. (0.36 mole) of N-chloromethylphthalimide, and 52 g. (0.39 mole) of anhydrous aluminum chloride in 500 ml. of 1,2,4-trichlorobenzene is slowly heated to 110° over a 2-hour period and then kept at that temperature for another 2 hours and 15 minutes. The cooled reaction mixture is poured over 500 g. of ice containing 30 ml. of concentrated hydrochloric acid, and the trichlorobenzene is removed by steam distillation. The glassy residue is boiled with 300 ml. of ethyl acetate, and the resulting crystalline solid is collected and washed successively with ethyl acetate and hot water. The dried product weighs 95 g. (97%), m.p. 248–249°. Recrystallization from a chloroform-ethanol mixture and then from glacial acetic acid gives pure 4-phthalimidomethyl-1-naphthol-8-sulfonic acid γ-sultone, m.p. 252–253°.

α-Benzoylamino-α-phenyl-o-cresol from Phenol and N,N′-Benzylidenebisbenzamide.[74] A mixture of 6.6 g. (0.02 mole) of the bisamide and 1.88 g. (0.02 mole) of phenol is heated for 4 hours at 180–190° in an oil bath. The brown, hard, resinous material is dissolved in glacial acetic acid, and the product is precipitated by the addition of water. The precipitate is collected, washed with water, and dried to give 4.2 g. (69%) of a yellow powder, m.p. 118°. The powder is dissolved in the minimum amount of ethyl acetate, filtered from a small quantity of insoluble material, and recovered once again by removal of the ethyl acetate. Four

³⁷⁹ Schetty, *Helv. Chim. Acta*, **31**, 1229 (1948).

recrystallizations from ethanol give pure α-benzoylamino-α-phenyl-*o*-cresol, m.p. 214°.

2-(α-Acetylaminobenzyl)-4-nitrophenol from 4-Nitrophenol, N,N′-Benzylidenebisacetamide, and Phosphorus Oxychloride.[18]
A mixture of 3.5 g. (0.025 mole) of 4-nitrophenol, 5.76 g. (0.028 mole) of the bisamide, and 1.84 g. (0.012 mole) of phosphorus oxychloride is heated (94–96°) on the steam bath for 1 hour. The cooled mixture is decomposed with water and neutralized with sodium bicarbonate. The resulting solid is collected, washed, and dried. Recrystallization from ethanol gives 5.8 g. (81%) of pure 2-(α-acetylaminobenzyl)-4-nitrophenol, m.p. 208–209°.

α-Amidoalkylation of Aliphatic Carbon Atoms

2-Benzamidomethylcyclohexane-1,3-dione (50) from N-Methylolbenzamide and Cyclohexane-1,3-dione.[85]
A solution of 2.24 g. (0.02 mole) of cyclohexane-1,3-dione and 3.02 g. (0.02 mole) of N-methylolbenzamide in 20 ml. of acetic acid is treated with 1.5 g. (0.01 mole) of boron trifluoride etherate. After 20 hours a first crop of crystals is obtained (scratching may be necessary) and collected. The filtrate is mixed with water containing 2.5 g. of sodium acetate, and a second crop of colorless crystals is obtained. The combined amount is 4.0 g. of crystals, m.p. 157–160°. The crude product is digested with 100 ml. of cold 1N sodium hydroxide and the insoluble by-product, methylenebisbenzamide, is removed by filtration. The filtrate is acidified with concentrated hydrochloric acid, and the resulting solid is collected and recrystallized from ethanol to give 3.2 g. (65%) of pure product, m.p. 162–164°.

N,N′-Bis-(β-trinitroethyl)fumaramide (54) from N,N′-Bis(benzoxymethyl)fumaramide and Trinitromethane.[93]
A mixture of 50 ml. of dry nitromethane, 0.38 g. (1.0 mmole) of N,N′-bis(benzoxymethyl)fumaramide, and 0.45 g. (3.0 moles) of trinitromethane is heated under reflux for 4 hours. The solvent is then removed in vacuum, and the solid residue is extracted with boiling carbon tetrachloride in order to remove the benzoic acid. The residue, which is insoluble in carbon tetrachloride, is dissolved in absolute ethanol, and water is added to the point of turbidity. On standing, 0.20 g. (47%) of product, m.p. 197° (dec.), crystallizes.

Diethyl Methylbenzamidomethylmalonate, $C_6H_5CONHCH_2$-$C(CH_3)(CO_2C_2H_5)_2$, from N-Chloromethylbenzamide and Diethyl Methylmalonate.[100]
A suspension of 4.2 g. (0.025 mole) of N-chloromethylbenzamide and 4.7 g. (0.024 mole) of diethyl sodiomethylmalonate in 20 ml. of dry diethyl ether is heated on a steam bath under reflux for 1

hour. The slimy precipitate is removed by filtration and washed with ether. The ether fractions are combined, and the ether is removed by distillation. The viscous yellow residue is distilled under reduced pressure. Any unchanged diethyl methyl malonate distils as the oil bath is heated to 180°. The fraction distilling at 180°/0.05 mm. is collected, and it eventually crystallizes as a white, waxy substance. It is recrystallized from diisoamyl ether to give 5.8 g. (78%) of product, m.p. 67°.

Diethyl α-Acetamidobenzylmalonate, $CH_3CONHCH(C_6H_5)$-$CH(CO_2C_2H_5)_2$, **from Benzylidenebisacetamide and Diethyl Malonate.**[115] A mixture of 10.3 g. (0.05 mole) of N,N'-benzylidenebisacetamide, 8 g. (0.05 mole) of diethyl malonate, and 25 ml. of acetic anhydride is heated for 3 hours in an oil bath at 150–155°. (Prolonged heating leads to diethyl benzylidenemalonate; e.g., after heating for 9 hours the yield drops to 11%.) The acetic anhydride is removed under reduced pressure (14 mm.), and 100 ml. of water is added with stirring to the remaining viscous mass. The colorless crystals that separate are collected and washed with cold water and a little diethyl ether. The dried product, m.p. 83°, weighs 8.9 g. An additional 0.7 g. is obtained from the ether filtrate (total yield: 9.6 g., 62%). Recrystallization from 50% ethanol gives the pure product, m.p. 85°. It is readily soluble in ethanol and acetone, sparingly soluble in ether, and insoluble in water.

Diethyl β-Benzamidomethyl-α-cyanopimelate (82) from N-(Diethylaminomethyl)benzamide and Diethyl α-Cyanopimelate.[118] A mixture of 2.4 g. (0.01 mole) of diethyl α-cyanopimelate, 2.06 g (0.01 mole) of N-(diethylaminomethyl)benzamide, 0.01 g. of powdered sodium hydroxide, and 30 ml. of toluene is heated at reflux under nitrogen. After 5 hours 80% of the theoretical quantity of diethylamine is evolved. The mixture is then cooled, and 100 ml. of petroleum ether is added. An oil separates which crystallizes after 3 days. This solid is recrystallized from petroleum ether to give 3.2 g. (85%) of the product 82, m p 61°.

β-Benzamido-β,β-diphenylpropionitrile from N-Benzoyldiphenylphenylketimine and Acetonitrile.[120] To a stirred solution of 1.49 g. (0.065 mole) of lithium amide in 200 ml. of liquid ammonia is added, during 5 minutes, a solution of 1 25 g (0 03 mole) of acetonitrile in 10 ml. of diethyl ether. The mixture is stirred for 15 minutes and then, over another 5 minute period, is added a solution of 8 60 g. (0.03 mole) of N-benzoyldiphenylketimine $[C_6H_5CON=C(C_6H_5)_2]$ in a mixture of benzene (100 ml.) and ether (50 ml.). After stirring for 1 hour, 3.50 g. of solid ammonium chloride is added, the ammonia is removed by distillation, and 100 ml. of water is added to the residue. The organic layer is separated, washed with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent by distillation give 8.40 g

(85%) of material, m.p. 132–134°. Recrystallization from ethanol gives pure product, m.p. 134–135°.

5-Carbethoxy-2-keto-6-methyl-4-phenyl-1,2,3,4-tetrahydro-pyrimidine (90) from Ethyl Acetoacetate, Benzaldehyde, and Urea.[126] A mixture of 53 g. (0.5 mole) of benzaldehyde, 30 g. (0.5 mole) of urea, 97.5 g. (0.75 mole) of ethyl acetoacetate, 200 ml. of absolute ethanol, and 40 drops of concentrated hydrochloric acid is heated under reflux for 3 hours. The mixture is then cooled to 0°, and the crystallized pyrimidine (93.6 g.) is collected and dried at 50°. The filtrate is heated under reflux for 2 hours and then distilled until 155 ml. of ethanol is collected. On cooling the residue an additional 21.3 g. of the pyrimidine is obtained, giving a total crude yield of 114.9 g. For purification the crude product is divided into two equal portions, and each is dissolved in 800 ml. of boiling 95% ethanol. On cooling, the pyrimidine separates to give 102 g. (78%) of colorless crystals, m.p. 202–204°. The loss on recrystallization may be materially decreased by distilling the solvent to incipient crystallization. The pyrimidine dissolves slowly in ethanol, and an excess of solvent is needed to effect solution.

Preparation of Some Electrophilic Reagents

N-Methyloltrifluoroacetamide, $CF_3CONHCH_2OH$.[259] Trifluoro-acetamide (4.4 g., 0.039 mole), potassium carbonate (0.16 g.), and formalin (3.2 ml., 0.042 mole) are mixed. A homogeneous solution forms, and the product crystallizes almost immediately. After refrigeration overnight the product is collected and recrystallized from chloroform to yield 4.95 g. (88%) of filamentary crystals. One more recrystallization from the same solvent gives N-methyloltrifluoroacetamide, m.p. 105–105.5°, with a satisfactory elemental analysis.

N-Methylolphthalimide.[54] A mixture of 511 g. (3.48 moles) of phthalimide, 260 ml. of 40% formaldehyde solution, and 1.75 l. of water is heated until a clear solution results. This requires only 5 minutes after the boiling point is reached. The solution is refrigerated overnight, the product is removed by filtration, washed with ice water, and air-dried. The yield of N-methylolphthalimide, m.p. 137–141°, is 594 g. (96%), and the product is sufficiently pure for most purposes. The material should not be dried at elevated temperatures because it loses formaldehyde. Recrystallization from ethanol does not improve the melting point.

If a pure sample is needed, the following procedure may be used.[122] A solution obtained by warming 17.7 g. of N-methylolphthalimide in 30 ml.

of pure pyridine is filtered, if necessary, and left to crystallize. If crystallization does not occur, seed crystals are obtained by placing a few drops of the solution in a desiccator over concentrated sulfuric acid. As soon as the first crystals appear, they are added to the solution. The pyridine complex crystallizes in long lustrous needles which are collected after cooling in an ice bath. On drying in vacuum over concentrated sulfuric acid, the crystals lose their luster and come to constant weight after 24 hours. The dried product melts at 148.5–149°, and one re-crystallization from acetone gives pure N-methylolphthalimide, m.p. 149.5°.

N-Chloromethyltrichloroacetamide.[186] A cold stirred solution of 19.2 g. (0.1 mole) of N-methyloltrichloroacetamide[264] in 10 ml. of dry diethyl ether is treated with a suspension of 20 g. (0.096 mole) of phosphorus pentachloride in 20 ml. of dry diethyl ether. After the initial reaction and evolution of hydrogen chloride moderates, the mixture is heated for 10 minutes under reflux and allowed to stand overnight. Ice water is then added dropwise to the cooled, stirred solution. The precipitate is collected and washed with ice water. Two recrystallizations from lukewarm carbon tetrachloride give 16 g. (76%) of N-chloromethyltrichloroacetamide, m.p. 76–77°.

N-Bromomethylphthalimide.[104] A mixture of 80 g. (0.45 mole) of N-methylolphthalimide, 150 ml. of 48% hydrobromic acid, and 45 ml. of concentrated sulfuric acid is stirred for 2 hours at 50–60°. The crystalline product is collected and washed with water and then with dilute aqueous ammonia to remove all acid. Drying at 80° gives 75 g. (69%) of N-bromomethylphthalimide, m.p. 146–147°. Recrystallization from acetone gives a purer product, m.p. 148°.

N-Acetoxymethylstearamide from Stearamide and Paraformaldehyde in Acetic Acid–Acetic Anhydride.[139] A solution of 200 g. (0.71 mole) of stearamide and 25 g. (0.83 mole) of paraformaldehyde in a mixture of 200 ml. of acetic anhydride and 400 ml. of glacial acetic acid is heated at 70° for 4 hours and then cooled. The precipitate is collected and dried. Recrystallization from acetone gives N-acetoxymethyl-stearamide, m.p. 92–93°, in 66% yield.

N,N′-Methylenebis-p-toluamide from p-Tolunitrile.[4] A solution of trioxane (1.5 g., .05 mole) in p-tolunitrile (11.7 g., 0.1 mole) is added slowly with stirring to 38 ml. of an 85% solution of sulfuric acid in a 125-ml. three-necked flask. The temperature is maintained at 30° by means of an ice bath. After 3 hours the solution is poured into 300 ml. of ice and water. The product separates as white crystals which are collected, washed with water, and recrystallized from 95% ethanol. The yield of N,N′-methylenebis-p-toluamide, m.p. 209–210°, is 12.4 g. (83%).

N,N′-Methylenebischloroacetamide from N–Methylolchloro-acetamide.[11] N-Methylolchloroacetamide (10 g., 0.081 mole) is dissolved in 25 g. of concentrated sulfuric acid with cooling. The solution is allowed to stand overnight and is then poured over ice. The precipitate is collected and the filtrate saturated with salt to obtain more of the product which is collected and combined with the main product. The yield of crude material is 95%. Recrystallization from 95% ethanol gives pure N,N′-methylenebischloroacetamide, m.p. 175°.

N,N′Benzylidenebisacetamide.[283] A solution of 10.6 g. (0.1 mole) of benzaldehyde and 11.8 g. (0.2 mole) of acetamide in 100 ml. of benzene is heated under reflux for 48 hours under a Soxhlet extractor containing 50 g. of anhydrous magnesium sulfate. The precipitate is filtered, washed with acetone, and recrystallized from ethanol to give a 72% yield of N,N′-benzylidenebisacetamide, m.p. 239.5°.

N,N′-Benzylidenebisbenzamide.[85] A mixture of freshly distilled benzaldehyde (21.2 g., 0.2 mole), benzamide (48.4 g., 0.4 mole), and freshly distilled acetic anhydride (50 ml.) is warmed until a clear solution results. Four drops of concentrated hydrochloric acid is added, and the solution is heated on a steam bath for 2 hours. The acetic anhydride is removed by distillation under reduced pressure, and the residue is taken up in hot ethanol. Cooling gives 51.7 g. (78%) of crystalline N,N′-benzylidenebisbenzamide, m.p. 231.5–232.5°.

Stearamidomethylpyridinium Chloride, $n\text{-}C_{17}H_{35}CONHCH_2^{\oplus}NC_5H_5Cl^{\ominus}$.[138] Stearamide (141 g., 0.5 mole) and paraformaldehyde (20 g., 0.67 mole) are added to a solution of 0.5 mole of pyridine hydrochloride in 2 l. of pyridine. The mixture is heated at 80° for 10 hours, cooled, and filtered. An equal volume of cold acetone is added to the filtrate, and the precipitate is collected and added to the original crop. The combined solids are recrystallized from acetone to yield 160 g. (78%) of stearamidomethylpyridinum chloride, melting at about 135°. The material sinters at 92°, and the final melting point varies with the rapidity of heating, probably because of partial conversion to methylenedistearamide.

TABULAR SURVEY

The tables fall into three groups. Tables I to VII summarize the α-amidoalkylation reactions of aromatic carbon atoms, Tables VIII to XIX those involving substitution at aliphatic carbon atoms, and Tables XX to XXXVI list the various electrophilic reagents that have been used in the α-amidoalkylation of carbon atoms.

The literature has been surveyed through 1962, but a number of more recent references have been included in both the text and the tables.

Exhaustive coverage has been attempted for the first two parts of this survey, but no such claim can be made for the third. The widely dispersed way in which these compounds appear in the literature makes omission of many examples a virtual certainty. Sufficient numbers have been listed, however, to provide a representative sampling of possible structural variation in the electrophilic reagent.

Because the N-aminomethylamides have been thoroughly reviewed recently,[3] Table XXVIII is intentionally incomplete. It is devoted exclusively to examples which were omitted from the review cited or which have been reported since its publication.

Within each table, reactions or reagents are arranged in order of increasing complexity of the amide portion of the amidoalkylating reagent. The nucleophilic substrates are generally arranged according to increasing complexity of substituent groups as listed in Heilbron's *Dictionary of Organic Compounds*.[381] Where applicable, the order aliphatic, aromatic, heterocyclic is also followed, but arylaliphatic aldehydes, acids, and amides are treated as derivatives of the aliphatic portion of the molecule. Compounds containing reactive methylene or methine groups are listed in the order nitro, aldehydo, keto, ester, polynitro, diketo, nitro ester, keto ester, diester, cyano, cyano ketone, and cyano ester.

Except where a separate column is provided for them, yields are given in parentheses after the references to which they relate.

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[381] Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, pp. xv–xvi.

TABLE I

Aminomethylation of Aromatic Carbon Atoms with N-Monomethylol Derivatives of Carboxamides and Carbamyl Compounds

$$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
HCONHCH$_2$OH and			
4-Nitrophenol	x-	Concd. H$_2$SO$_4$	22
CH$_3$CONH(CH$_2$OH and			
4-Nitrophenol	x,x-	Concd. H$_2$SO$_4$	23
2-Naphthol	1-	HCl, C$_2$H$_5$OH	96 (95)
Thiophene	2-	85 % H$_3$PO$_4$, 90°	49 (50)
Ethyl 2,5-dimethylpyrrole-3-carboxylate	4-	HCl, C$_2$H$_5$OH	17
CH$_3$CON(CH$_3$)CH$_2$OH and			
Benzene	1-	BF$_3$, C$_6$H$_6$	32 (68)
2-Naphthol	1-	HCl, C$_2$H$_5$OH	32 (94)
CH$_3$CON(C$_3$H$_7$-n)CH$_2$OH and			
2-Naphthol	1-	HCl, C$_2$H$_5$OH	32
CH$_2$ClCONHCH$_2$OH and			
Benzene	1-	Concd. H$_2$SO$_4$	13 (88)
Chlorobenzene	2- and 4-	Concd. H$_2$SO$_4$	13 (80)
Phenol	4-	AlCl$_3$, CH$_3$CO$_2$H	51
2-Nitrophenol	4-	Concd. H$_2$SO$_4$	11 (90)
4-Nitrophenol	2-	Concd. H$_2$SO$_4$	11 (90), 20
Catechol	x-	3 % HCl, H$_2$O	11
Hydroquinone	x,x-	1 % HCl, C$_2$H$_5$OH	11 (20)
Pyrogallol	x,x-	1 % HCl, C$_2$H$_5$OH	11 (15)

Compound	Position	Reagent	References (Yield %)
4-Nitroveratrole	2,6-	Concd. H_2SO_4	11 (80)
Guaiacol	4-	20% H_2SO_4, C_2H_5OH	11, 382
Veratrole	4-	$AlCl_3$, CH_3CO_2H	51 (64)
1,2,3-Trimethoxybenzene	4- and 2,4-	$ZnCl_2$, CH_3CO_2H	52
1,2,4-Trimethoxybenzene	4-	$ZnCl_2$, CH_3CO_2H	52
Acetanilide	5-	$ZnCl_2$, CH_3CO_2H	52
	4-	Concd. H_2SO_4	11 (100), 20
4-Hydroxyacetanilide	4-	$AlCl_3$, CH_3CO_2H	51 (16)
Acetp-phenetidine	4-	Concd. H_2SO_4	11 (70)
4-($C_6H_4OH)COXH)C_6H_4OC_2H_5$	4-	Concd. H_2SO_4	11 (70)
Toluene	4-	H_2SO_4, CH_3CO_2H	13 (75)
	2,4-	70% H_2SO_4	13 (50)
m-Xylene	4,6-	Concd. H_2SO_4	13 (47)
p-Xylene	2-	H_2SO_4, CH_3CO_2H	13 (94)
Thymol	4-	H_2SO_4, CH_3CO_2H	13 (35)
Phenylacetic acid	4-	Concd. H_2SO_4	13 (92)
Cinnamic acid	3- and 4-	1% HCl, C_2H_5OH	11 (20)
Benzoic acid	6-	Concd. H_2SO_4 or HF	47 (35)
2-Chlorobenzoic acid	x,x-	Concd. H_2SO_4	21 (68)
Salicylic acid	2(?)-	Concd. H_2SO_4	11 (54), 20
3,4,5-Trimethoxybenzoic acid	x,x,x-	Concd. H_2SO_4	57 (65)
o-Toluic acid	3(?)-	$ZnCl_2$, CH_3CO_2H	11 (40), 20
p-Toluic acid	3-	Concd. H_2SO_4	52
Tetralin	x,x-	Concd. H_2SO_4	7
	x,x,x-	Concd. H_2SO_4	7
Naphthalene	x,x-	H_2SO_4, CH_3CO_2H	13 (39)
	x,x,x-	H_2SO_4, CH_3CO_2H	13 (46)
		H_2SO_4, CH_3CO_2H	13 (85)
		Concd. H_2SO_4	13 (28)
2-Naphthol	1-	Satd. HCl, C_2H_5OH	13 (81)
2-Methoxynaphthalene	1-	Satd. HCl, C_2H_5OH	26 (60)

TABLE I—*Continued*

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$CH_3CONHCH_2OH$ (contd.) and			
1-Hydroxy-2-naphthoic acid	4-	H_2SO_4, CH_3CO_2H	40
2-Hydroxy-3-naphthoic acid	1-	H_2SO_4, CH_3CO_2H	40
9-Fluorenone	2,7-	Concd. H_2SO_4	7
2-Nitro-9-fluorenone	7-	Concd. H_2SO_4	7
9,10-Phenanthrenequinone	2(?)-	Concd. H_2SO_4	7
7H-Benz[de]anthracen-7-one (benzanthrone)	3,9(?)-	Concd. H_2SO_4	7
Methyl 2-furoate	5-	Concd. H_2SO_4	35 (100)
Ethyl 2-furoate	5-	Concd. H_2SO_4	383
	5-	PPA,* CH_3CO_2H	48 (51)
2-Thiophenecarboxylic acid	4(?)-	Concd. H_2SO_4	56 (53)
Ethyl 2,4-dimethylpyrrole-3-carboxylate	5-	HCl, C_2H_5OH	17 (good)
Ethyl 2,5-dimethylpyrrole-3-carboxylate	4-	HCl, C_2H_5OH	17 (good)
Acridine	x-	Concd. H_2SO_4	384
3-Methyl-1-phenyl-5-pyrazolone	4-	Concd. H_2SO_4	11
2,3-Dimethyl-1-phenyl-5-pyrazolone (antipyrine)	4-	$AlCl_3$, CH_3CO_2H	51 (70)
	4-	100% H_3PO_4, CH_3CO_2H	48 (48)
$CCl_3CONHCH_2OH$ and			
2-Hydroxybenzophenone	3,5(?)-	Concd. H_2SO_4	7
4-Hydroxybenzophenone	3,5(?)-	Concd. H_2SO_4	7
2,4-Dimethylbenzophenone	5(?)-	Concd. H_2SO_4	7
o-Toluic acid	5(?)-	Concd. H_2SO_4	7
p-Toluic acid	3-	Concd. H_2SO_4	7
2,4-Dimethylbenzoic acid	5-	Concd. H_2SO_4	7

0-Fluorenone	2,7-	Concd. H₂SO₄	7
2-Nitro-9-fluorenone	7-	Concd. H₂SO₄	7
2-Hydroxy-9-fluorenone	7-	Concd. H₂SO₄	7
2-Acetamido-9 fluorenone	7-	Concd. H₂SO₄	7
1,2-Acenaphthenequinone	4-	Concd. H₂SO₄	385
1-Hydroxyanthraquinone	4-	Concd. H₂SO₄	37, 385, 386
2-Hydroxyanthraquinone	1-	Concd. H₂SO₄	37, 385
2-Hydroxy-1-chloroanthraquinone	4-	Concd. H₂SO₄	39
2-Hydroxy-3-chloroanthraquinone	1-	Concd. H₂SO₄	37, 387
1,2-Dihydroxyanthraquinone	2,4,6,8-	Concd. H₂SO₄	36, 37
1,5-Dihydroxyanthraquinone	2,4,5,7-	Concd. H₂SO₄	385
1,8-Dihydroxyanthraquinone	1,4-	Concd. H₂SO₄	385
2,3-Dihydroxyanthraquinone		Concd. H₂SO₄	385
1-Hydroxy-2-methylanthraquinone	4-	Concd. H₂SO₄	37, 385
1-Hydroxy-3-methylanthraquinone		Concd. H₂SO₄	37, 385
1,3-Dimethylanthraquinone		Concd. H₂SO₄	385
2-Hydroxyanthraquinone-3-carboxylic acid		Concd. H₂SO₄	
9,10-Phenanthrenequinone	2(?)- and 2/7(?)-	Concd. H₂SO₄	
2-Nitro-9,10-phenanthrenequinone	7(?)-	Concd. H₂SO₄	
2-Hydroxy-9,10-phenanthrenequinone	7(?)- and 3/7(?)-	Concd. H₂SO₄	
3H-benz[de]anthracen-7-one (brazanthrone)	3,9(?)-	Concd. H₂SO₄	
3 Hmra 7H benz[de]anthracen-7 one	9(?)-	Concd. H₂SO₄	
3 Hmra 7H benz[de]anthracen-7 one	9(?)-	Concd. H₂SO₄	
Xanthen 9 one	2(?)- and 2,4,5,7(?)-	Concd. H₂SO₄	
C₆H₅CON(CH₂CON(CH₃)₂OH and p (?cresol)	2-	1% HCl, C₂H₅OH	70
2-Naphthol	1-	HCl, C₂H₅OH	79
C₆H₅CON(CH₂CON(CH₃)₂OH and 2-Naphthol	1-	HCl, C₂H₅OH	79

Note: References 382 to 537 are on pp. 266-269.
*Polyphosphoric acid.

TABLE I—*Continued*

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$C_6H_5CONHCH_2OH$ and N,N-Dimethylaniline	4(?)-	HCl, C_2H_5OH	388
p-Cresol	2-	1 % HCl, C_2H_5OH	79
2-Naphthol	1-	1 % HCl, C_2H_5OH	388 (84)
6-Bromo-2-naphthol	1-	1 % HCl, C_2H_5OH	388 (85)
3,6-Dibromo-2-naphthol	1-	HCl, C_2H_5OH	388 (80)
$C_6H_5CH_2CONHCH(CH_3)CONHCH_2OH$ and 2-Naphthol	1-	HCl, C_2H_5OH	79
$C_6H_5CH_2CH_2CONHCH_2OH$ and 2-Naphthol	1-	HCl, C_2H_5OH	79
N-Methylol-2-pyrrolidinone and 2-Naphthol	1-	HCl, C_2H_5OH	33 (50)
$(CH_3)_2CHCH_2CONHCH_2OH$ and 2,4-Xylenol	6-		54
3,3-Bis(p-hydroxyphenyl)oxindole (phenolisatin)	x- and x,x-	$ZnCl_2$, CH_3CO_2H	53
n-$C_7H_{15}CONHCH_2OH$ and 3,3-Bis(p-hydroxyphenyl)oxindole (phenolisatin)	x- and x,x-	$ZnCl_2$, CH_3CO_2H	53
3,3-Bis(p-hydroxyphenyl)phthalide (phenolphthalein)	x,x-	$ZnCl_2$, CH_3CO_2H, 50°	53

n-C₃H₇CONHCH₂OH and			
Phenol	4(?)-	AlCl₃, CH₃CO₂H	51 (63)
Guaiacol	4-	AlCl₃, (CH₃)₂CO	51 (73)
n-C₄H₉CONHCH₂OH and			
Guaiacol	4-	AlCl₃, CH₃CO₂H	51 (65)
	4-	100% H₃PO₄, (CH₃)₂CO	48 (61)
CH₂=CH(CH₂)₈CONHCH₂OH and			
Catechol	4-	HCl, C₂H₅OH	389 (2)
Guaiacol	4-	20% H₂SO₄, C₂H₅OH	382, 390
	4-	AlCl₃, CH₃CO₂H	51 (63)
CH₃(CH=CH)₄CONHCH₂OH and			
Catechol	4-	HCl, C₂H₅OH	389 (57)
C₆H₅CONHCH₂OH and			
Benzene	1-	H₂SO₄, CH₃CO₂H	13
Phenol	1,4-	Concl. H₂SO₄	13 (32)
	4(?)-	AlCl₃, (CH₃)₂CO	51 (60)
	4(?)-	100% H₃PO₄, CH₃CO₂H	48 (66)
2-Nitrophenol	2-	Concl. H₂SO₄	10
4-Nitrophenol	2-	HCl, CH₃OH	1,10 (90), 20
Catechol	z,z-	Concl. H₂SO₄	1 (<90), 20
Hydroquinone	z,z-	Concl. H₂SO₄	1 (<90), 20
Pyrogallol	4-	HCl, CH₃CO₂H	10 (30)
Guaiacol	4-	HCl, C₂H₅OH	10 (20)
4-Nitroveratrole	5-	HCl, C₂H₅OH	10 (33)
1,2,3-Trimethoxybenzene	4- and 4,5-	HCl, C₂H₅OH	10 (<25), 382 (27)
		AlCl₃, (CH₃)₂CO	51 (68)
		Concl. H₂SO₄	68 (31)
		Concl. H₂SO₄	52
	4- and 4,5-	ZnCl₂, CH₃CO₂H	52

Note: References 382 to 537 are on pp. 206–209.

TABLE I—*Continued*

Aminomethylation of Aromatic Carbon Atoms with N-Monomethylol Derivatives of Carboxamides and Carbamyl Compounds

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$C_6H_5CONHCH_2OH$ (*contd.*) and			
N,N-Dimethylaniline	4-	HCl, C_2H_5OH	388 (26)
Acetanilide	4-	Concd. H_2SO_4	13 (82)
Toluene	4-	H_2SO_4, CH_3CO_2H	13 (90)
p-Cresol	2-	HCl, C_2H_5OH	79
2,4-Xylenol	6-	HCl, C_2H_5OH	55
Thymol	4-	H_2SO_4, C_2H_5OH	10 (82)
Benzoic acid	3-	Concd. H_2SO_4	10 (8), 20
o-Toluic acid	5(?)-	Concd. H_2SO_4	7
p-Toluic acid	3-	Concd. H_2SO_4	7
1-Hydroxyphenylarsonic acid	3-	Concd. H_2SO_4	391
2-Naphthol	1-	HCl, C_2H_5OH	1, 10 (100), 20
6-Bromo-2-naphthol	1-	HCl, C_2H_5OH	388 (90)
3,6-Dibromo-2-naphthol	1-	HCl, C_2H_5OH	388
2-Methoxynaphthalene	1-	HCl, CH_3OH, 40°	392 (97)
2-Hydroxy-3-naphthoic acid	1-	H_2SO_4, CH_3CO_2H	40
Fluorene			86
9-Fluorenone	2,7-	Concd. H_2SO_4	7
1-Hydroxyanthraquinone	4- and 2,4-	Concd. H_2SO_4	37, 385
2-Hydroxyanthraquinone	1-	Concd. H_2SO_4	36, 37, 385
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	37
1,8-Dihydroxyanthraquinone	2,4,5-	Concd. H_2SO_4	385
1,3-Dimethylanthraquinone	2-	Concd. H_2SO_4	7 (0)
2-Hydroxy-9,10-phenanthrenequinone	7(?)-	Concd. H_2SO_4	7

		7
7H-Benz[de]anthracen-7-one (benzanthrone)	3-	Concd. H_2SO_4	393 (30)
2-Furoic acid	5-	Concd. H_2SO_4	35 (100)
Methyl 2-furoate	5-	Concd. H_2SO_4	383
Ethyl 2-furoate	5-	Concd. H_2SO_4	56
2-Thiophenecarboxylic acid	4-	Concd. H_2SO_4	394
6-Hydroxyquinoline	x-	Concd. H_2SO_4	10, 394
8-Hydroxyquinoline	x-	Concd. H_2SO_4	394
2-Hydroxy-6-methoxy-4-methylquinoline	x-	Concd. H_2SO_4	86
Carbazole			384
Acridine	x-	Concd. H_2SO_4	86
Rhodanine		$AlCl_3$, $(CH_3)_2CO$	51 (32)
2,3-Dimethyl-1-phenyl-5-pyrazolone (antipyrene)	4-	$AlCl_3$, H_2SO_4	86
Perolonic acid	4-		86
4-Methyl-2-thiouracil	5-	Concd. H_2SO_4	395
o-$O_2NC_6H_4CONHCH_2OH$ and 2-Furoic acid	5-	Concd. H_2SO_4	393
o-$HOC_6H_4CONHCH_2OH$ and Catechol	x-, x-	HCl, C_2H_5OH	25 (56)
Hydroquinone	x-, x-	HCl, C_2H_5OH	25 (56)
Pyrogallol	x-	HCl, C_2H_5OH	25 (100)
Phenetole	4-	$AlCl_3$, $C_2H_5O\cdot C_2H_5$, $C_2H_5O_2H$	51 (63)
Thymol	x-	HCl, C_2H_5OH	25 (56)
p-$CH_3C_6H_4CONHCH_2OH$ and 2-Furoic acid	5-	Concd. H_2SO_4	393
N-Methylol-2-furamide and N-Methylol-2-furamide	2,5-Polymer	Heat, pressure	35

Note: References 382 to 537 are on pp. 205–209.

TABLE I—*Continued*

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF
CARBOXAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylol-β-2-furanacrylamide and N-Methylol-β-2-furanacrylamide	2,5-Polymer	Heat, pressure	36
$C_6H_5O_2CNHCH_2OH$ and 2,4-Xylenol	6-	HCl, C_2H_5OH	218 (56)
$(CH_3)_2NCONHCH_2OH$ and 3,3-Bis-(p-hydroxyphenyl)oxindole (phenolisatin)	x,x-	$ZnCl_2$, CH_3CO_2H, 50°	53
$CO(NHCH_2OH)_2$† and Phenol	2-	HCl	38 (50)
2-Nitrophenol	4-	H_2SO_4, CH_3CO_2H	40
4-Nitrophenol	2-	H_2SO_4, CH_3CO_2H	40
1-Hydroxyanthraquinone	2-	Concd. H_2SO_4	37
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	36, 37, 39
$C_6H_5NHCONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H, 50°	54
p-$CH_3C_6H_4NHCONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H, 50°	55

Note: References 382 to 537 are on pp. 206–209.
† Reacting as a monomethylolamide. For bifunctional reactions see Table III.

TABLE II

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylolsuccinimide and 4-Nitroveratrole	5-	Concd. H_2SO_4	58 (1,4)
N-Methylolmaleimide and 2-Nitrotoluene	1(?)-	Concd. H_2SO_4	8 (12)
N-Methylolsuccinimide and 4-Methyl-2-thionaftol	5-	Concd. H_2SO_4	305
N-Methylolphthalimide and benzene			
Mirbenzene	1-	Concd. H_2SO_4	16
	3-	Oleum	16
	3,5-	20% Oleum	20
Phenol	4-	Concd. H_2SO_4	10
4-Nitrophenol	2-	Oleum	15
2,4-Dinitrophenol	2-, 4-, and 2,4-	Concd. H_2SO_4	15
4-Nitroveratrole	6-	Concd. H_2SO_4	16
Aniline	3- and 4-	5% Oleum, Dr	60 (95)
N,N-Dimethylaniline	4-	Concd. H_2SO_4	58 (89)
Acetanilide	4(?)-	4% Oleum	11 (>80)
	3- (27%) and 4- (60%)	Oleum	16
	3- (11%), and 4- (33%), and 2,4- (27%)	95% H_2SO_4	398 (41)
	4- (6%) and 2,4- (90%)	99.5% H_2SO_4	44 (87)
		1.5% Oleum	11 (75)
2-Nitrotoluene		4% Oleum	11 (72)
3-Nitrotoluene	5(?)-	Concd. H_2SO_4	16 (95)
4-Nitrotoluene	2-	Concd. H_2SO_4	16
	2,6-	Concd. H_2SO_4	29 (95)
α-Toluamide	3,5-	Concd. H_2SO_4	29 (77)

Note: References 382 to 537 are on pp. 266-269.

TABLE I—*Continued*

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylol-β-2-furanacrylamide and N-Methylol-β-2-furanacrylamide	2,5-Polymer	Heat, pressure	35
$C_3H_5O_2CNHCH_2OH$ and 2,4-Xylenol	6-	HCl, C_2H_5OH	218 (56)
$(CH_2)_2NCONHCH_2OH$ and 3,3-Bis-(p-hydroxyphenyl)oxindole (phenolisatin)	x,x-	$ZnCl_2$, CF_3CO_2H, 50°	53
$CO(NHCH_2OH)_2$† and Phenol	2-	HCl	38 (50)
2-Nitrophenol	4-	H_2SO_4, CH_3CO_2H	40
4-Nitrophenol	2-	H_2SO_4, CH_3CO_2H	40
1-Hydroxyanthraquinone	2-	Concd. H_2SO_4	37
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	36, 37, 39
$C_6H_5NHCONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H, 50°	54
p-$CH_3C_6H_4NHCONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H, 50°	55

Note: References 382 to 537 are on pp. 266-269. For bifunctional reactions see Table III.

† Reacting as a monomethylolamide.

TABLE II

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	Reference (Yield, %)
N-Methylolsuccinimide and 4-Nitroveratrole	5-	Concd. H_2SO_4	58 (1.4)
N-Methylolmaleimide and 2-Nitrotoluene	4(?)	Concd. H_2SO_4	8 (12)
N-Methylolsaccharin and 4-Methyl-2-thiouracil	5-	Concd. H_2SO_4	395
N-Methylolphthalimide and			
Benzene	1-	Concd. H_2SO_4	16
Nitrobenzene	3-	Oleum	16
	3,5-		29
Phenol	2, 4, and 2,4-	Concd. H_2SO_4	16
		20% Oleum	16
4-Nitrophenol	2-	Concd. H_2SO_4	15
2,4-Dinitrophenol	6-	Concd. H_2SO_4	16
4-Nitroveratrole	5-	5% Oleum, 95°	69 (95)
Aniline	3- and 4-	Concd. H_2SO_4	58 (88)
		4% Oleum	44 (>60)
N,N-Dimethylaniline	4(?)	Concd. H_2SO_4	16
Acetanilide	4(?)	95% H_2SO_4	396 (41)
	2- (27%) and 4- (60%)	99.5% H_2SO_4	44 (87)
	2- (15%) and 2,4- (33%), and 2,4- (27%)	1.5% Oleum	44 (75)
2-Nitrotoluene	4- (6%) and 2,4- (66%)	4% Oleum	44 (72)
3-Nitrotoluene	5(?)	Concd. H_2SO_4	16 (95)
4-Nitrotoluene		Concd. H_2SO_4	16
o-Toluidine	2,6-	Concd. H_2SO_4	29 (95)
	3,5-	Concd. H_2SO_4	29 (77)

Note: References 392 to 537 are on pp. 286-299.

TABLE II—Continued

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylolphthalimide (contd.) and			
p-Toluidine	3-	98.3% H_2SO_4	44 (81)
	3,5-	Concd. H_2SO_4	29 (95)
4-Methylacetanilide	2- (3%) and 3- (17%)	99.5% H_2SO_4	44 (>20)
	2- (23%) and 3- (55%)	97.7% H_2SO_4	44 (>78)
2,4-Xylidine	3,5-	90% H_2SO_4	29
4-Phenylphenol	2-	H_2SO_4, C_6H_6	397 (>30)
4-Hydroxyacetophenone	3-	Concd. H_2SO_4	69 (92)
2-Methylbenzophenone	3,5(?)-	Concd. H_2SO_4	7
4-Methylbenzophenone	3(?)-	Concd. H_2SO_4	7
2,4-Dimethylbenzophenone	5(?)- and 3,5(?)-	Concd. H_2SO_4	7
Phenylacetic acid	3- and 4-	Concd. H_2SO_4	47 (85)
Benzoic acid	3-	95% H_2SO_4	396 (40)
	3-	Concd. H_2SO_4	12 (80)
o-Toluic acid	5(?)-	Concd. H_2SO_4	7
m-Toluic acid	6-	Concd. H_2SO_4	7
p-Toluic acid	3-	Concd. H_2SO_4	7
4-HOC$_6$H$_4$AsO$_3$H	1-	Concd. H_2SO_4	398
2-Naphthol	1-	88% H_2SO_4	396 (53)
9-Fluorenone	2,7-	Concd. H_2SO_4	7
1-Hydroxyanthraquinone	2,4-	Concd. H_2SO_4	37, 385
2-Hydroxyanthraquinone	1-	Concd. H_2SO_4	36, 37, 385
2-Hydroxy-3-chloroanthraquinone	1-	Concd. H_2SO_4	387
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	37,39
1,5-Dihydroxyanthraquinone	4(?)-	Concd. H_2SO_4	385
1,8-Dihydroxyanthraquinone	2,4,5,7-	Concd. H_2SO_4	385
2,3-Dihydroxyanthraquinone	1,4-	Concd. H_2SO_4	385
1,4-Di-(4'-methylanilino)anthraquinone	3', 5', 3'', 5''(?)-	96% H_2SO_4	399 (97)
1-Amino-2-bromo-4-(4'-methylanilino)-anthraquinone	3'(?)- and 3', 5'(?)-	96% H_2SO_4	399 (100)

1,4,5,8-Tetra-(4'-methylanilino)anthraquinone	3', 5', 3', 5', 5', 5'(†).	98% H_2SO_4	399 (97)
1-Hydroxy-2-methylanthraquinone	4-	Conel. H_2SO_4	37, 385
2-Hydroxy-3-methylanthrequinone	1-	Conel. H_2SO_4	37, 385
1,3-Dimethylanthraquinone	1-	Conel. H_2SO_4	7
2-Hydroxyanthraquinone-3-carboxylic acid	1-	Conel. H_2SO_4	385
1-(2'-Methyl-5'-chloroanilino)anthraquinone-2-carboxylic acid	4'(†)	90% H_2SO_4	399 (95)
1-Amino-4-(4'-methylanilino)anthraquinone-2-sulfonic acid	3'(†).	90% H_2SO_4	399
9,10-Phenanthrenequinone	2(†)- and 2,7(†)-	Conel. H_2SO_4	7, 400
2-Hydroxy-9,10-phenanthrenequinone	7(†)- and 3,7(†)-	Conel. H_2SO_4	7
2-Acetyl-9,10-phenanthrenequinone	7(†)-	Conel. H_2SO_4	7
7H-Benz[de]anthracen-7-one (benzanthrone)	3(†)-	90% H_2SO_4	400, 401 (100)
	3(†)-	90% H_2SO_4	7
	3,9(†).	Conel. H_2SO_4	400 (97)
	3,9(†).	66% H_2SO_4, 80°	7, 400
3-Bromo-7H-benz[de]anthracen-7-one	9(†)-	66% H_2SO_4, 80°	402 (100)
4,4'-Ilus-7H-benz[de]anthracen-7-one	3,3'(†)-	96% H_2SO_4	400 (95)
Dibenz[a,l]pyrene-7,14-dione (Indanthren Golden Yellow GK)	12(†)-	10% Oleum, 60°	403 (93)
Dibenz[e,l]pyrene-6,12-dione (anthanthrone)	10(†)-	10% Oleum, 60°	7
	3(†)-*	10% Oleum	403
Dinaphtho[1,2,3-cd:1',2',3'-lm]perylene-5,10-diono (violanthrone)	5-	10% Oleum	403 (100)
	5-	Conel. H_2SO_4	7
Ethyl 2-furoate	5-	Conel. H_2SO_4	383
4-Methyl-2-thiouracil	5-	Conel. H_2SO_4	395
Quinoline	5-(21%) and 8-(20%)	Conel. H_2SO_4	404 (41)
Cobalt phthalocyanine	z,z-	100% H_2SO_4, 75°	405
Copper phthalocyanine	z,z- to 8z	3% Oleum, 100°	64
		H_2SO_4, H_3PO_4, or P_2O_5	50
Cobalt monochlorophthalocyanine		100% H_2SO_4, 75°	405

Note. References 388 to 537 are on pp. 260–269.

* Sulfonation also occurred in the 12(†) position.

TABLE III

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH N,N'-DIMETHYLOL
DERIVATIVES OF DICARBOXAMIDES AND OF UREA

$(CH_2)_n(CONHCH_2OH)_2 + 2ArH \rightarrow (CH_2)_n(CONHCH_2Ar)_2$

and

$CO(NHCH_2OH)_2 + 2ArH \rightarrow CO(NHCH_2Ar)_2$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$(CONH(CH_2OH)_2$ and			
Methyl 2-furoate	5-	Concd. H_2SO_4	35 (88)
Ethyl 2-furoate	5-	Concd. H_2SO_4	35 (92)
$(CH_2)_3(CONHCH_2OH)_2$ and			
4-Nitrophenol	2-	Concd. H_2SO_4	20, 24
2,4-Xylenesulfonic acid	x-	Concd. H_2SO_4	20
2-Naphthol	1-	HCl, C_2H_5OH	20, 24
$(CH_2)_4(CONHCH_2OH)_2$ and			
Benzene	1-	Concd. H_2SO_4	406
4-Nitrophenol	2-	Concd. H_2SO_4	406 (80)
Acetanilide	4-	Concd. H_2SO_4	406 (41)
2-Methylacetanilide	x-	Concd. H_2SO_4	406
4-Methylacetanilide	x-	Concd. H_2SO_4	406 (55)
2-Naphthol	1-	Concd. H_2SO_4	406 (50)
2-Acetylaminonaphthalene	x-	Concd. H_2SO_4	406
$(CH_2)_3(CONHCH_2OH)_2$ and			
Benzene	1-	Concd. H_2SO_4	406 (37)
$(CH_2)_4(CONHCH_2OH)_2$ and			
Benzene	1-	Concd. H_2SO_4	406 (48)

TABLE IV

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH FORMALDEHYDE AND NITRILES OR AMIDES

$$RCN \; (or \; RCONH_2) + CH_2O + ArH \xrightarrow{H_2SO_4 \; or \; H_3PO_4} RCONHCH_2Ar$$

Product from Formaldehyde	Position(s) of Substituent(s)	Method	References (Yield, %)
HCN and m-Xylene	4-	H₂SO₄, CH₃CO₂H, 90°	5 (25)
CH₃CN and			
Benzene	4-	H₂SO₄, CH₃CO₂H, 90°	5 (50)
Bromobenzene	4-	Concd. H₂SO₄	5 (37)
Anisole	4-	H₂SO₄, CH₃CO₂H	5 (28)
Toluene	4-	H₂SO₄, CH₃CO₂H, 90°	5 (53)
Ethylbenzene	2- (10 %) and 4- (36 %)	H₂SO₄, CH₃CO₂H	5 (19)
Cumene	4-	H₂SO₄, CH₃CO₂H	5 (75)
o-Xylene	x-	H₂SO₄, CH₃CO₂H	5 (54)
m-Xylene	4-	H₂SO₄, CH₃CO₂H	5 (52)
	4,6-	85 % H₃PO₄, 90°	5 (66)
p-Xylene	4,6-	H₂SO₄, CH₃CO₂H, 90°	5 (75)
1,2,4-Trimethylbenzene	4,6-	H₂SO₄, CH₃CO₂H, 90°	5 (66)
N-(2,4-Dimethylbenzyl)acetamide	2- (21 %) and 2,5- (55 %)	H₂SO₄, CH₃CO₂H, 90°	5 (52)
	5-	H₂SO₄, CH₃CO₂H, 90°	5 (54)
1,2,4,5-Tetramethylbenzene (durene)	5-	H₂SO₄, CH₃CO₂H, 90°	5 (75)
	3,6-	H₂SO₄, CH₃CO₂H, 85°	5 (19)
Naphthalene	1- (12 %), 1,4- (25 %) and 1,5(?)- (6 %)	H₂SO₄, CH₃CO₂H, 90°	5 (45)
			5 (72)
			5 (>43)
CH₂ClCN and m-Xylene	4,6-	H₂SO₄, CH₃CO₂H	5
CH₂BrCH₂CN and m-Xylene	4,6-	H₂SO₄, CH₃CO₂H	5

CH₂=CHCN and		
Toluene	4-	H₂SO₄, CH₃CO₂H	5 (89)
Cumene	4-	H₂SO₄, CH₃CO₂H	5 (53)
m-Xylene	4,6-	85 % H₃PO₄, 90°	5
C₆H₅CN and		
m-Xylene	4,6-		5
2-Pyrrolidinone and		
4-Nitrotoluene	4,6-	H₂SO₄, CH₃CO₂H	5
γ-Valerolactam and		
4-Nitro-1,3-xylene	2-	Concd. H₂SO₄	34 (37)
Succinimide and		
4-Nitrotoluene	6-	Concd. H₂SO₄	34 (41)
Copper phthalocyanine	2-	Concd. H₂SO₄	34 (81)
4-Cyclohexene-1,2-dicarboximide and	x-	95 % H₂SO₄, 75°	50
4-Chloronitrobenzene	3-	Concd. H₂SO₄	34
Phthalimide and		
Copper phthalocyanine	x-	H₂SO₄, oleum, or P₂O₅	34 (75)
Urea and		
2,4-Xylenol	x- to z,z,z-	H₂SO₄, oleum, or P₂O₅	50

$$H_2NCONH_2 \text{ and } HSNHCONH_2$$

$$\left(R = \begin{array}{c} CH_3 \\ \\ OH \\ \\ CH_3 \end{array} \right)$$

Sulfanilamide and		
4-Methyl-2-thiourea	5-	HCl, CH₃CO₂H, heat	60
N,N-Acetylsulfanilamide and		
4-Methyl-2-thiourea	5-	HCl, CH₃CO₂H, heat	60
		HCl, CH₃CO₂H, heat	60

Note: References 382 to 537 are on pp. 200–209.

CH₂=CHCN and			
Toluene	4-	H₂SO₄, CH₃CO₂H	5 (89)
Cumene	4-	H₂SO₄, CH₃CO₂H	5 (53)
m-Xylene	4,6-	85% H₃PO₄, 90°	5
C₆H₅CN and			
m-Xylene	4,6-	H₂SO₄, CH₃CO₂H	5
2-Pyrrolidinone and			
4-Nitrotoluene	2-	Concd. H₂SO₄	34 (37)
γ-Valerolactam and			
4-Nitro-1,3-xylene	6-	Concd. H₂SO₄	34 (41)
Succinimide and			
4-Nitrotoluene	2-	Concd. H₂SO₄	34 (81)
Copper phthalocyanine	z-	95% H₂SO₄, 75°	50
4-Cyclohexene-1,2-dicarboximide and			
4-Chloronitrobenzene	3-	Concd. H₂SO₄	34 (75)
Phthalimide and			
Copper phthalocyanine	z- to z,z,z,-	H₂SO₄ oleum, or P₂O₅	50
Urea and			
2,4-Xylenol		HCO₂H, 50°	59

$$ H_2NCONH_2 \text{ and } RNHCONH_2 \qquad \left(R = \begin{array}{c} OH \\ CH_3- \\ CH_3 \end{array} \right) $$

Sulfanilamide and			
4-Methyl-2 (thiourea?)	5-	HCl, CH₃CO₂H, heat	60
N⁴-Acetylsulfanilamide and			
4-Methyl-2 thiouracil	5-	HCl, CH₃CO₂H, heat	60
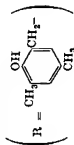
Note: References 382 to 537 are on pp. 266–269.

TABLE V

AMINOMETHYLATION OF AROMATIC CARBON ATOMS WITH ETHERS OF N-METHYLOL-AMIDES AND -IMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
[(CH$_3$)$_2$CHCH$_2$CONHCH$_2$]$_2$O and 2,4-Xylenol	6-	H$_2$SO$_4$, C$_2$H$_5$OH	54
o-C$_6$H$_4$(CO)$_2$NCH$_2$OCH$_3$ and Copper phthalocyanine	x,x-	100% H$_2$SO$_4$, 100°	64
o-C$_6$H$_4$(CO)$_2$NCH$_2$OC$_2$H$_5$ and Benzene	1-	100% H$_2$SO$_4$, 90°, 1.5 hr.	63 (5)
Nitrobenzene	3-	100% H$_2$SO$_4$, 80°, 1.5 hr.	63 (41)
[o-C$_6$H$_4$(CO)$_2$NCH$_2$]$_2$O and Phenol	x- and x,x-	Concd. H$_2$SO$_4$	61
4-Nitrophenol	2-	Concd. H$_2$SO$_4$	61
2-Nitrotoluene	5(?)-	Concd. H$_2$SO$_4$	61
Copper phthalocyanine	x-	100% H$_2$SO$_4$, 75°	50
(HOCH$_2$NHCONHCH$_2$)$_2$O and 2,4-Xylenol	RNHCONR$_2$, (RNH$_2$CO, and RNHCONH$_2$ R= [structure]	HCl, C$_2$H$_5$OH, 50°	62
(C$_2$H$_5$NHCONHCH$_2$)$_2$O and 2,4-Xylenol	6-	HCO$_2$H, 50°	54
(C$_6$H$_5$NHCONHCH$_2$)$_2$O and 2,4-Xylenol	6-	HCO$_2$H, 50°	54 (90)

Note: References 382 to 537 are on pp. 206-209.

TABLE VI

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-HALOMETHYL-AMIDES, -IMIDES, AND -CARBAMYL COMPOUNDS

$$RCONR'CH_2X + ArH \rightarrow RCONR'CH_2Ar$$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
CH₂CON(CH₃)CH₂Cl and			
Benzene	1-	AlCl₃, C₆H₆	32
4-Chlorophenol	2-	AlCl₃	32
Anisole	4-	AlCl₃	32
Toluene	4-	AlCl₃, C₆H₅CH₃	32 (92)
CH₂CON(C₆H₅,n)CH₂Cl and			
Benzene	1-	AlCl₃, C₆H₆	32
CH₂CON(CH₂C₆H₅)CH₂Cl and			
Toluene	4-	AlCl₃, C₆H₅CH₃	32
n-C₄H₉CON(CH₃)CH₂Cl and			
Phenol		CH₃CO₂H, 20–60°	67
C₆H₅CON(CH₃)CH₂Cl and			
Toluene	4-	AlCl₃, C₆H₅CH₃	32
1,4-Dichloromethylpiperazine-2,5-dione* and			
Benzene		AlCl₃, CS₂	65 (43)
Naphthalene	1-	No solvent, 160°	65 (64)
2-Naphthol	1-	C₂H₄, 80°	65 (89)
N-Chloromethylleucenamide and			
Benzene	1-	AlCl₃, CS₂	66

Note: References 382 to 537 are on pp. 210–269.
* Bifunctional reaction.

TABLE VI—*Continued*

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-HALOMETHYL-AMIDES,
-AMIDES, AND -CARBAMYL COMPOUNDS

$RCON(R')CH_2X + ArH \rightarrow RCON(R')CH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Chloromethylmaleimido and			
Benzene	1-	$ZnCl_2$, 80°	8 (83)
Phenol	2,4-	$ZnCl_2$, C_6H_6, 80°	8 (40)
o-$C_6H_4(CO)_2NCH_2Cl$ and			
Benzene	1-	$ZnCl_2$, C_6H_6	68
Phenol	2- and 4-	$ZnCl_2$, C_6H_6	68
Anisole	4-	$ZnCl_2$, 120°	68 (100)
	2- and 4-	$ZnCl_2$, 130°	378 (85)
n-$C_3H_7OC_6H_5$	4-	$ZnCl_2$, 150°	407
4-Chlorophenol	2-	$ZnCl_2$, 90–130°	69 (70)
Guaiacol	4-	No catalyst, 120°	68
2-Nitrotoluene	4-	$ZnCl_2$, 120°	68
m-Xylene	5-	$ZnCl_2$, 100°	68
N-(2,4-Dimethylbenzyl)phthalimide	5-	$ZnCl_2$, $C_6H_5NO_2$, 100°	68
Naphthalene	1-	$ZnCl_2$, melt	68
N-(1-Naphthylmethyl)phthalimide	4,8(?)-	$ZnCl_2$, $C_6H_5NO_2$, 120°	68
1-Naphthol-8-sulfonic acid γ-sultone	4-	$AlCl_3 \cdot C_6H_3Cl_3$, 110°	370 (97)
Anthracene	9,10-	$ZnCl_2$, $C_6H_5NO_2$, 100°	68
7H-Benz [de] anthracen-7-one (benzanthrone)	3(?)-	$ZnCl_2$, $C_6H_5NO_2$, 140°	408, 409
Copper phthalocyanine	5a-	$AlCl_3$, piperidine, 140°	64
	a,a-	100% H_2SO_4, 80°	64
Copper tetraphenylphthalocyanine	6a-	$AlCl_3$, pyridine, 130°	64
	4a-	Concd. H_2SO_4	64

α-C₆H₄(CO)₂NCH₂Br and

Benzene	1-	ZnCl₂, 80°	14 (94)
Phenol	2- and 4-	C₆H₆, no catalyst, 80°	15 (50)
	2(?)-	Heat, no solvent	70
Thymol	4-	Heat	71 (62)
Phenylacetic acid	4-	Heat	71 (69)
2-Naphthol	z-	ZnCl₂, 120°	47 (10)
ClCON]CH₂Cl and	z-	Heat	71 (63)
Phenol			

structure		Pentane, 40°, 3 hr.	73 (5)

2,4-Dichloroaniline		Heptane, 25°, 16 hr.	73 (65)

2,4-(CH₃)₂C₆H₃CH₂NCO
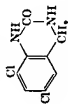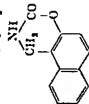
m-Xylene		ZnCl₂, CH₂Cl₂, 58°	73 (35)
β-Naphthol		Pentane, 25°, 24 hr.	73 (25)

Note: References 342 to 537 are on pp. 266-269.

TABLE VII

α-Amidoalkylation of Aromatic Carbon Atoms with N,N'-Methylene-, -Alkylidene-, and -Arylidene-bisamides

$$(RCONH)_2CHR' + ArH \rightarrow RCONHCH(R')Ar + RCONH_2$$

(R' = H, alkyl, or aryl)

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
(HCONH)₂CH₂ and 2,4-Xylenol	6-	POCl₃, 95°, 1 hr.	75 (38)
(CH₃CONH)₂CH₂ and Phenol	2- (25%) and 4- (21%)	POCl₃, CHCl₃, 65°, 4 hr.	76, 77 (>40)
4-Nitrophenol	2-	POCl₃, 95°, 1 hr.	18 (85)
Anisole	4- (46%) and o,o- (26%)	POCl₃, 95°, 3 hr.	77 (72)
4-Methoxytoluene	3-	POCl₃, 95°, 1 hr.	18 (93)
2-Methylacetanilide	4-	POCl₃, 130°, 1 hr.	18 (80)
4-Methylacetanilide	2-	POCl₃, 130°, 1 hr.	18 (71)
2,4-Xylenol	6-	POCl₃, 95°, 1 hr.	75 (94)
Salicylic acid	5-	POCl₃, 95°, 1 hr.	76, 78 (>30)
2-Naphthol	1-	POCl₃, CHCl₃, 65°	18 (94)
8-Hydroxyquinoline	5-	POCl₃, 95°, 1 hr.	18 (84)
(CH₃CH₂CONH)₂CH₂ and 2,4-Xylenol	6-	POCl₃, 95°, 1 hr.	75 (80)
(C₆H₅CONH)₂CH₂ and Benzene	1-	100% H₂SO₄, 95°, 6 hr.	63 (63)
2,4-Xylenol	6-	POCl₃, 95°, 1 hr.	75 (93)
o-C₆H₄(CO)₂NCH₂NHCOC₆H₅ and Benzene	1-	100% H₂SO₄, 90°, 5.5 hr.	63 (24)*
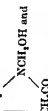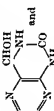
(C₆H₅NHCOSH)₂CH₂ and 2,4-Xylenol	6-	HCO₂H, 50°	55
(p-CH₃C₆H₄NHCOSH)₂CH₂ and 2,4-Xylenol	6-	HCO₂H, 50°	55
(CH₂CONH)₂CH₂C₆H₄ and p-Cresol	2-	POCl₃, C₆H₆, 80°	18 (93)
2,4-Xylenol	6-	POCl₃, C₆H₆, 80°	75 (74)
2-Naphthol	1-	POCl₃, CHCl₃, 65°	18 (91)
(CH₂CONH)₂CHC₆H₄ and Phenol	2-	190°, 4 hr.	74 (41)
Phenyl acetate	2-	190°, 4 hr.	74 (43)
4-Nitrophenol	2-	POCl₃, 95°, 1 hr.	18 (81)
p-Cresol	2-	190°, 4 hr.	74 (49)
4-Methoxytoluene	3-	POCl₃, 95°, 1 hr.	18 (91)
2-Methylacetanilide	3-	POCl₃, 95°, 2 hr.	18 (91)
4-Methylacetanilide	4-	POCl₃, 130°, 2 hr.	18 (88)
2,4-Xylenol	6-	POCl₃	76
2,6-Xylenol	4-	POCl₃, 95°, 1.5 hr.	75 (98)
2-Naphthol	1-	190°, 4 hr.	74 (74)
		190°, 4 hr.	74 (30)
		POCl₃, C₆H₆, 80°, 1.5 hr.	18 (98)
		190°, 4 hr.	74 (93)
(C₆H₅NHCONH)₂CHC₆H₄ and Phenol			
Phenyl benzoate	2-	190°, 4 hr.	74 (09)
	2-	190°, 4 hr.	74 (12)
2-Naphthol	1-	190°, 4 hr.	74 (93)

Note. References 283 to 327 are on pp. 205–209.

* The only product obtained was N-benzylphthalimide.

TABLE VIII

α-Amidoalkylation of Aliphatic Carbon Atoms with N-Monomethylol and N-α-Alkylol Derivatives of Amides, Imides, and Carbamyl Compounds

Product Derived from	Method	References (Yield, %)
HCONHCH₂OH and Trinitromethane	H₂O	88
CH₃CONHCH₂OH and Trinitromethane	H₂O, pH 7, 70°, 10 min.	88 (75)
CH₂ClCONHCH₂OH and Cyclohexane-1,3-dione	H₂SO₄, 3 days	85 (0)
(O₂N)₃CCH₂CH₂CONHCH₂OH and Trinitromethane	CH₃OH, 12 hr.	87 (80)
CH₃—CHCONHCH₂OH and Trinitromethane	H₂O, 5°, 48 hr.	87 (5)
	C₂H₅OH, CH(NO₂)₃ (2 equiv.), 12 hr.	87 (88)*
CH₃—C(CH₃)CONHCH₂OH and Trinitromethane	H₂O, 1 day	87 (87)
C₆H₅CONHCH₂OH and Trinitromethane	H₂O, 80°	88
Cyclohexane-1,3-dione	Concd. H₂SO₄, 3 days	85 (36)
	C₂H₅OH, concd. HCl, 3 days	85 (20)
	CH₃CO₂H, ZnCl₂, 3 days	85 (40)
	CH₃CO₂H, BF₃-etherate, 20 hr.	85 (65)
5,5-Dimethylcyclohexane-1,3-dione	H₂SO₄, 25°, 3 days	85†
1-Phenylbutane-1,3-dione	C₂H₅OH	86
1,3-Diphenylpropane-1,3-dione	Concd. H₂SO₄, 40 hr.	86
	CH₃CO₂H, BF₃-etherate, 20 hr.	85 (74)
x-O₂NC₆H₄CONHCH₂OH and Trinitromethane	H₂O	88

o-C₆H₄(CO)₂NCH₂OH and		
Pentane-2,4-dione	Concd. H₂SO₄, 0°, 1 day	85 (85)
5,5-Dimethylcyclohexane-1,3-dione	H₂SO₄, 1 day	85 (74)
1-Phenylbutane-1,3-dione	Concd. H₂SO₄, 1 day	85 (83)
1,3-Diphenylpropane-1,3-dione	Concd. H₂SO₄, 1 day	85 (84)
Ethyl acetoacetate	Concd. H₂SO₄, cold, 1 day	85‡
Malonic acid	H₂SO₄, standing overnight	84 (0)
Diethyl malonate	H₂SO₄, 2 days	85 (0)
	H₂SO₄, 3 days	84 (0)
1,2-Diphenylpyrazolidine-3,5-dione	Concd. H₂SO₄, 1 day	85 (83)
$\begin{array}{c}CH_2CO\\ \qquad\ NCH_2OH\ and\\ CH_2CO\end{array}$		
Cyclohexane-1,3-dione	H₂SO₄, 3 days	85 (0)
C₆H₄O₂NCH(CH₃)OH and Trinitromethane	H₂O, 80° short reaction time	88 (90)
CH₃NHCONHCH₂OH and Trinitromethane	H₂O	88
$\begin{array}{c}CHOH\\ NH\\ CO\\ NH\end{array}$ and		
Acetone	H₂O, NaHCO₃, 5 hr.	89 (0)
Pentane-2,4-dione	H₂O, K₂CO₃, 1 day	89 (75)
Ethyl acetoacetate	H₂O, K₂CO₃, 20 hr.	89 (80)
Diethyl malonate	No solvent, 100°, 4 hr	89 (90)
Ethyl cyanoacetate		89 (90)

Note   References 382 to 537 are on pp. 266–269.
* Trinitromethane added to its carbon-carbon double bond during the amidoalkylation. The product was the saturated material (O₂N)₃CCH₂CH₂CONHCH₂C(NO₂)₃.
† The product was not characterized.
‡ Mono- (33%) and bis- (16%) amidoalkylation occurred with concomitant decarboxylation.
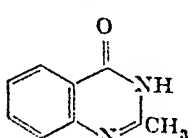
TABLE IX
Amidomethylation of Aliphatic Carbon Atoms with Dimethylol Derivatives of Fumaramide and of Urea

Product Derived from	Method	References (Yield, %)
HOCH$_2$NHCOCH $\parallel$ HCCONHCH$_2$OH and Trinitromethane	H$_2$O, pH 0.8, 90 min.	87 (48)
CO(NHCH$_2$OH)$_2$ and Trinitromethane	H$_2$O, 40°, 5 min.	88 (77)
	Urea, formalin (2 equiv.), 22 hr.	88 (88)
Acetylene	10 atm., 40°, 10–20 hr.	90

Note: References 382 to 537 are on pp. 266–269.

TABLE X
α-Amidoalkylation of Aliphatic Carbon Atoms with Formaldehyde or Acetaldehyde and Sulfonamides

Product Derived from	Method	References
CH$_3$(CH$_2$)$_2$CH$_2$SO$_2$NH$_2$, CH$_2$O, and Potassium cyanide	Aq. CH$_2$O, 80°, 1 hr.	91
CH$_3$(CH$_2$)$_6$CH$_2$SO$_2$NH$_2$, CH$_2$O, and Potassium cyanide	Aq. CH$_2$O, 45°, 2 hr.	91
C$_6$H$_5$SO$_2$NH$_2$ and HOCH$_2$CN	8 % NaOH, 90°, 1 hr.	91
C$_6$H$_5$SO$_2$NH$_2$, CH$_2$O, and Sodium cyanide	Aq. CH$_2$O, 70°, 2 hr.	91
C$_6$H$_5$SO$_2$NH$_2$, CH$_3$CHO, and Potassium cyanide	H$_2$O, 95°, 2 hr.	91
p-H$_2$NC$_6$H$_4$SO$_2$NH$_2$, (CH$_2$O)$_x$, and 2-Picoline	Paraffin oil, 130°	92
Quinaldine	Paraffin oil, 130°	92
9-Methylacridine	Paraffin oil, 180°	92
9-Ethylacridine	Paraffin oil, 130°	92
(quinazolinone structure)	No solvent, 160–170°	92
p-CH$_3$CONHC$_6$H$_4$SO$_2$NH$_2$, (CH$_2$O)$_x$, and 2-Picoline	Paraffin oil, 200°	92
p-CH$_3$C$_6$H$_4$SO$_2$NH$_2$, CH$_2$O, and Sodium cyanide	H$_2$O, 70°, 2 hr.	91

Note: References 382 to 537 are on pp. 266–269.

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TABLE XI

α-Amidoalkylation of Aliphatic Carbon Atoms with Ethers and Esters of N-Methylol- and N-α-Alkylol-Amide Derivatives

Product Derived from	Method*	References (Yield, %)
$(C_2H_5O_2CNHCHCHCCl_3)_2O$ and Diethyl malonate	KOC_2H_5, ether, 0°	94 (35), 95
$C_2H_5O_2CNHCH(OCOCH_2)CCl_3$ and Potassium cyanide	H_2O, 0°, 3–4 hr.	94 (53)†
CH_2=CHCONHCH$_2$OCOC$_6$H$_5$ and Trinitromethane	$(CH_3Cl)_3$, 1 equiv., reflux, 0.5 hr	93 (4)‡
	CH_3NO_2, 2 equiv., 101°, 15 min.	93 (49)‡
	CH_3NO_2, 101°, 0.5 hr	93 (12)‡
	$(CH_3Cl)_3$, 2 equiv., 83°, 0.5 hr.	93 (43)‡
	C_2H_5OH, 2 equiv., 78°, 0.5 hr.	93 (35)‡
	H_2O, 2 equiv., 25°, 4 hr.	93 (10)‡
CH_2=C(CH$_3$)CONHCH$_2$OCOC$_6$H$_5$ and Trinitromethane	$(CH_3Cl)_3$, 25°, 12 hr	93 (50)
	H_2O, 25°, 0.5 hr	93 (64)
	$(CH_3Cl)_3$, 2 equiv., 25°, 3 hr.	93 (65)
$CH_3CO_2CH_2NHCOCH$ $HCCONHCH_2OCOCH_3$ and Trinitromethane	H_2O, reflux, 25 min.	93 (2)
$C_6H_5CO_2CH_2NHCOCH$ $HCCONHCH_2OCOC_6H_5$ and Trinitromethane	CH_3NO_2, reflux, 4 hr	93 (47)

Note: References 382 to 537 are on pp. 266–269

* The abbreviation "equiv." refers to the number of equivalents of trinitromethane

† The product obtained was of the type $C_2H_5O_2CNHC(CN)$—CCl_3

‡ Trinitromethane added to the carbon carbon double bond during amidoalkylation. The product was the saturated material $[O_2N)_3CCH_2CH_2CONHCH_2]NO_2)_3$

TABLE XII

α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N-HALOMETHYL AND N-α-HALOALKYL DERIVATIVES OF
AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

Product Derived from	Method*	References (Yield, %)
HCONHCH₂Cl and Diethyl methylmalonate	Dioxane	96, 100 (20)
HCONHCHClCCl₃ and Diethyl malonate	(C₂H₅)₂O, reflux, 3–4 hr.	160
CH₃CONHCH₂Cl and Diethyl malonate	Dioxane, 50°, 1 hr.	96, 100 (25)
Diethyl methylmalonate	Dioxane, 70°, 1.5 hr.	100 (31)
Ethyl cyanoacetate	Dioxane, 70°, 1 hr.	96, 100 (27)
CH₃CON(CH₃)CH₂Cl and Diethyl methylmalonate	Dioxane, 40°, 30 min.	98 (68)
CH₃CON(C₃H₇-n)CH₂Cl and Diethyl methylmalonate	Dioxane, 100°, 1 hr.	98 (38)
CH₃CON(C₃H₇-i)CH₂Cl and Diethyl methylmalonate		98 (28)
CH₂ClCONHCH₂Cl and Diethyl methylmalonate	Dioxane	96
CCl₃CONHCH₂Cl and 1-Phenylbutane-1,3-dione	Dioxane	96 (51)
Diethyl ethylmalonate	(C₂H₅)₂O, reflux, 15 min.	100 (62)
α-Phenylacetoacetonitrile	Dioxane	96 (57)
1-Chloromethyl-2-pyrrolidinone and Diethyl methylmalonate	Dioxane-acetonitrile, 40°, 2 hr.	33 (40)
N-Chloromethyl-ε-caprolactam and Diethyl methylmalonate	Dioxane, 100°, 0.5 hr.	33 (40)
C₆H₅CONHCH₂Cl and Pentane-2,4-dione	(C₂H₅)₂O	96 (60)†
3-Methylpentane-2,4-dione	(C₂H₅)₂O, reflux, 2 hr.	410 (88)
Ethyl acetoacetate	(C₂H₅)₂O, reflux, 0.5 hr.	96, 100 (57)
Ethyl α-methylacetoacetate	(C₂H₅)₂O, reflux, 0.5 hr.	96, 100 (50)
Ethyl α-isopropylacetoacetate	(C₂H₅)₂O, reflux, 0.5 hr.	96, 100 (50)
2-Carbethoxycyclohexanone	Dioxane, 100°, 3 hr.	96 (84)
Dimethyl malonate	(C₂H₅)₂O	96 (81)†
Diethyl methylmalonate	(C₂H₅)₂O, reflux, 1 hr.	96, 100 (77)
Diethyl ethylmalonate	(C₂H₅)₂O, reflux, 0.5 hr.	96 (72), 100 (72)
Ethyl α-cyanopropionate	(C₂H₅)₂O, reflux, 1 hr.	96 (48), 100 (48)
1-Phenylbutane-1,3-dione	(C₂H₅)₂O, reflux, 0.5 hr.	96 (51), 100
α-Phenylacetoacetonitrile	(C₂H₅)₂O, reflux, 1.5 hr.	96 (79), 100 (51)
C₆H₅CON(CH₃)CH₂Cl and Ethyl methylacetoacetate	Dioxane, 100°, 1 hr.	98 (28)
Diethyl methylmalonate	Dioxane, 100°, 1 hr.	98 (37)
C₆H₅CONHCHClCCl₃ and 1-Phenylbutane-1,3-dione	Dioxane, 50°, 3 hr.	101 (73)

Note: References 382 to 537 are on pp. 266–269.
* Unless otherwise noted, the sodium salt of the active methylene compound was prepared before the alkylating agent was added.
† The bisamidoalkylated product was obtained.

TABLE XII—*Continued*

α-Amidoalkylation of Aliphatic Carbon Atoms with
N-Halomethyl and N-α-Haloalkyl Derivatives of
Amides, Lactams, Imides, and Carbamyl Compounds

Product Derived from	Method[a]	References (Yield, %)
2,4 $Cl_2C_6H_3CONHCH_2Cl$ and Diethyl methylmalonate	Dioxane	96
2-CH_2O-5 $ClC_6H_3CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	107 (ca 39)‡
2-CH_2O-3,5 $Cl_2C_6H_2CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	107 (ca 39)‡
2-CH_2O-5-$BrC_6H_3CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	107 (ca 39)‡
2-CH_2O-3,5-$Br_2C_6H_2CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	107 (ca 39)‡
m-$CH_3C_6H_4CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	106‡
p-$CH_3C_6H_4CONHCHClCCl_3$ and Potassium cyanide	CH_3COCH_3, 0 hr.	106‡
o $C_6H_4(CO)_2NCH_2Cl$ and Diphenylacetaldehyde	$(C_2H_5)_2O$	97
2-Methyl-1-phenylbutane-1,3 dione	CH_3COCH_3, reflux, 30 min	97 (54)
Cyclohexane-1,3-dione	CH_3OH/C_6H_6, reflux	85 (20)
1,1,4-Trimethylcyclohexano-3,5-dione	C_2H_5OH, reflux, 30 min.	97 (96)
Ethyl α-methylacetoacetate	$(C_2H_5)_2O$	97 (63)
Diethyl methylmalonate	Dioxane	97 (47)
Diethyl ethylmalonate	$(C_2H_5)_2O$	97 (81)
Diethyl acetamidomalonate	C_2H_5OH	97 (67)
Diethyl phenylmalonate	$(C_2H_5)_2O$	97 (60)
α-Phenylacetoacetonitrile	C_2H_5OH/CH_3COCH_3, reflux 30 min	97 (83)
o $C_6H_4(CO)_2NCH_2Br$ and 3-Phenyl-2-benzofuranone	$(C_2H_5)_2O$, reflux, 2-3 hr	105 (73)
Ethyl acetoacetate	C_2H_5OH	104 (0)
Ethyl 4,4-diethoxyacetoacetate	C_2H_5OH, reflux, 3 hr	104 (0)
Diethyl malonate	C_2H_5	104 (0)
Potassium cyanide	CH_3COCH_3, reflux, 3 hr	104 (0)
N-Chloromethylsaccharin and Ethyl methylacetoacetate	$(C_2H_5)_2O$, reflux, 3 hr	99 (36)
Diethyl methylmalonate	$(C_2H_5)_2O$, reflux, 4 hr	99 (39)
Ethyl methylcyanoacetate	$(C_2H_5)_2O$, reflux, 3 hr	99 (41)
$C_2H_5O_2CNHCHClCCl_3$ and Ethyl acetoacetate	$(C_2H_5)_2O$, reflux, 6 7 hr	160

Note: References 382 to 537 are on pp. 266 269.

[a] Unless otherwise noted, the sodium salt of the active methylene compound was prepared before the alkylating agent was added.

‡ The product was of the type $ArCONHC(CN)$—CCl_3

TABLE XIII

α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N,N'-METHYLENEDISULFONAMIDES AND N,N'-ETHYLIDENE-
BISURETHAN OR THEIR PRECURSORS

Method A: $(ArSO_2NH)_2CH_2 + HC{<} \rightarrow ArSO_2NHCH_2C{<} + ArSO_2NH_2$

Method B: $C_2H_5O_2CNH_2 + CH_3CHO + HC{<} \rightarrow C_2H_5O_2CNHCH(CH_3)C{<}$
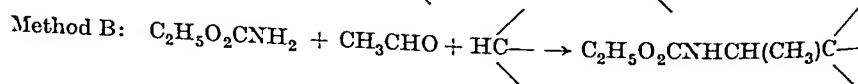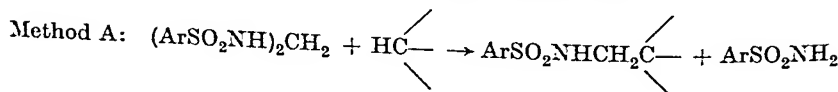
Product Derived from	Method	References (Yield, %)
$(C_6H_5SO_2NH)_2CH_2$ and Cyclohexane-1,3-dione	A; H_2SO_4, 25°, 2 days	85 (18)
$(p\text{-}CH_3C_6H_4SO_2NH)_2CH_2$ and Cyclohexane-1,3-dione	A; H_2SO_4, 25°, 2 days	85 (19)
$C_2H_5O_2CNH_2$, CH_3CHO, and Pentane-2,4-dione	B; C_2H_5OH, HCl, 24 hr.	108 (30)

Note: References 382 to 537 are on pp. 266–269.

TABLE XIV

α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH N,N-ARYLIDENEBISAMIDES OR THEIR PRECURSORS

Method A: $(RCONH)_2CHAr + HC \rightarrow RCONHCH(Ar)C + RCONH_2$

Method B: $RCONH_2 + ArCHO + HC \rightarrow RCONHCH(Ar)C$
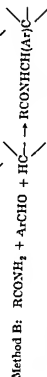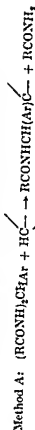
Product Derived from	Method	References (Yield, %)
Acetamide, benzaldehyde, and Nitromethane	A; $(CH_3CO)_2O$, 100°, 24 hr.	113 (32)
Cyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr.	85 (0)
5,5-Dimethylcyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr.	85 (12)
Ethyl nitroacetate	A; $(CH_3CO)_2O$, 100°, 7 hr.	112 (85)
Ethyl acetoacetate	B; $(CH_3CO)_2O$, 100°, 7 hr.	112 (61)
Dimethyl malonate	A; $(CH_3CO)_2O$, 120°, 5 hr.	114 (72)
Diethyl malonate	A; $(CH_3CO)_2O$, HCl, 155°, 3 hr.	85 (62)
	A; $(CH_3CO)_2O$, 155°, 3 hr.	115 (62)
Diethyl ethylmalonate	A; 180°, 9 hr.	115 (51)
Hippuric acid	A; $(CH_3CO)_2O$, 155°, 5 hr.	116 (76)
	A; CH_3CO_2H, $(CH_3CO)_2O$, 110°	117 (61)*

Note: References 382 to 537 are on pp. 266–269.

* The product was

$$CH_3\text{-}CONHCH(C_6H_5)CH\text{---}C=O$$

(with the structure showing a ring containing N, O, and C_2H_5)
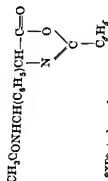
All other alkylations of hippuric acid gave the expected products.

TABLE XIV—*Continued*

α-AMINOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N,N'-ARYLIDENEBISAMIDES OR THEIR PRECURSORS

Method A: $(RCONH)_2CHAr + HC\diagdown \rightarrow RCONHCH(Ar)C\diagdown + RCONH_2$

Method B: $RCONH_2 + ArCHO + HC\diagdown \rightarrow RCONHCH(Ar)C\diagdown$

Product Derived from	Method	References (Yield, %)
Acetamide, benzaldehyde (*contd.*) and CH_2CH_2CO, NH, S, CS (piperazine-2,5-dione)	A; $(CH_3CO)_2O$, 150°, 2 hr.	411 (93)
Piperazine-2,5-dione	A; $(CH_3CO)_2O$, 165°, 12 hr.	100 (29)†
Acetamide, o-nitrobenzaldehyde, and Ethyl nitroacetate	B; $(CH_3CO)_2O$, 100°, 7 hr.	112 (12)
Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$	117 (0)
Acetamide, p-nitrobenzaldehyde, and Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$	117 (0)
Acetamide, o-methoxybenzaldehyde, and Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$, heat, 1 hr.	117 (57)‡
Acetamide, p-methoxybenzaldehyde, and Diethyl malonate	A; $(CH_3CO)_2O$, 155°, 3 hr.	115 (45)
Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$, heat, 1 hr.	117 (40)‡
Acetamide, veratraldehyde, and Ethyl nitroacetate	A; $(CH_3CO)_2O$, 100°, 7 hr. B; $(CH_3CO)_2O$, 100°, 7 hr.	112 (44) 112 (41)
Ethyl acetoacetate	A; $(CH_3CO)_2O$, 130°, 8 hr.	114 (76)

Acetamide, piperonal, and		
Ethyl nitroacetate	B; $(CH_3CO)_2O$, 100°, 8.5 hr.	112 (40)
Ethyl acetoacetate	A; $(CH_3CO)_2O$, 120°, 5 hr.	114 (50)
Diethyl malonate	A; $(CH_3CO)_2O$, 155°, 3 hr.	115 (53)
Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$, heat, 1.5 hr.	117 (50)‡
Acetamide, O-acetylvanillin, and		
Ethyl nitroacetate	A; $(CH_3CO)_2O$, 100°, 7 hr.	112 (51)
	B; $(CH_3CO)_2O$, 100°, 7 hr.	112 (40)
Acetamide, p-tolualdehyde, and		
Hippuric acid	A; CH_3CO_2H, $(CH_3CO)_2O$, heat, 1.5 hr.	117 (55)‡
Benzamide, benzaldehyde, and		
Cyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 140°, 4 hr.	85 (40)
5,5-Dimethylcyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr.	85 (0)
Ethyl nitroacetate	A; $(CH_3CO)_2O$, 135°, 2 hr.	85 (47)
Dimethyl malonate	A; $(CH_3CO)_2O$, 155°, 3 hr.	85 (52)
Benzamide, o-nitrobenzaldehyde, and		
Cyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr	85 (0)

$$CH_3CONHCH(C_6H_5)$$
74

Note: References 382 to 537 are on pp. 266–269.

† The product was
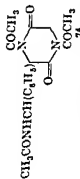
‡ This yield is based on the combined weight of the stereoisomeric products $CH_3CONHCH(Ar)CH(CO_2H)NHCOC_6H_5$ (73).

TABLE XIV—*Continued*

α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N,N'-ARYLIDENEBISAMIDES OR THEIR PRECURSORS

Method A: $(RCONH)_2CHAr + HC\diagdown \rightarrow RCONHCH(Ar)C\diagdown + RCONH_2$

Method B: $RCONH_2 + ArCHO + HC\diagdown \rightarrow RCONHCH(Ar)C\diagdown$
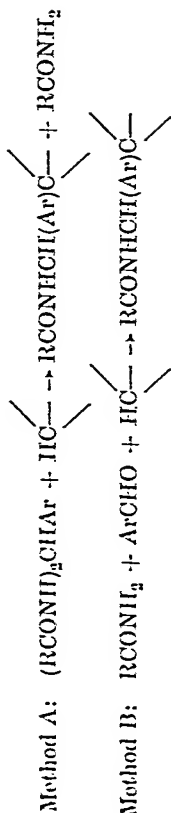
Product Derived from	Method	References (Yield, %)
Ethyl carbamate, acetaldehyde, and Pentane-2,4-dione	B; HCl, C₂H₅OH	108
Ethyl carbamate, cinnamaldehyde, and Pentane-2,4-dione	B; HCl, C₂H₅OH	111
Ethyl acetoacetate	B; HCl, C₂H₅OH	111
Ethyl carbamate, benzaldehyde, and Pentane-2,4-dione	B; HCl, C₂H₅OH	111
Ethyl acetoacetate	B; HCl, C₂H₅OH	111
Ethyl benzoylacetate	B; HCl, C₂H₅OH	111
Ethyl carbamate, salicylaldehyde, and Pentane-2,4-dione	B; HCl, C₂H₅OH	111
Ethyl carbamate, p-methoxybenzaldehyde, and Pentane-2,4-dione	B; HCl, C₂H₅OH	111

Note: References 382 to 537 are on pp. 206–260.

TABLE XV

AMIDOMETHYLATION OF ALIPHATIC CARBON ATOMS WITH N-AMINOMETHYLAMIDES AND THEIR QUATERNARY SALTS

Product Derived from	Method	References (Yield, %)
$C_6H_5CONHCH_2N(CH_3)_2$ and		
Nitrocyclohexane	Toluene, NaOH, reflux, 50 hr.	118 (38)
Dimethyl acetamidomalonate	Toluene, NaOH, reflux, 2.5 hr.	118 (87)
Diethyl methylmalonate	Toluene, NaOH, reflux, 5.5 hr.	118 (48)
Diethyl benzylmalonate	Toluene, NaOH, reflux, 11.5 hr.	118 (63)
Diethyl phenylmalonate	Toluene, NaOH, reflux, 1 hr.	118 (100)
$C_6H_5CONHCH_2N(C_2H_5)_2$ and		
1,3-Diphenylpropane-1,3-dione	Toluene, $N(C_4H_9\text{-}n)_4$, reflux, 30 hr.	118 (3)
Ethyl α-ethylacetoacetate	Toluene, NaOH, reflux, 30 hr.	118 (33)
Dimethyl malonate	Toluene, NaOH, reflux, 3 hr.	118 (68)
Diethyl ethylmalonate	Toluene, NaOH, reflux, 7 hr.	118 (44)
$C_2H_5O_2C(CH_3)CH(CN)CO_2C_2H_5$	Toluene, NaOH, reflux, 5 hr.	118 (85)
Ethyl α-phenylcyanoacetate	Toluene, NaOH, reflux, 8 hr.	118 (74)
$o\text{-}C_4H_4(CO)_2NCH_2N(CH_3)_2$ and		
Diethyl malonate	No solvent, NaOH, 100°, 5–15 hr.	81 (0)
Diethyl acetamidomalonate	Xylene, reflux	1*
$o\text{-}C_4H_4(CO)_2NCH_2N$ and		
Diethyl formamidomalonate	Xylene, 150°, 4 hr.	81 (0)
$o\text{-}C_4H_4(CO)_2NCH_2\overset{\oplus}{N}(CH_3)_3$ $I^{\ominus}$ and		
Cyclohexane-1,3-dione	CH_3OH, Na, reflux, 6 hr.	85 (0)
Diethyl malonate	C_2H_5OH, $NaOC_2H_5$, reflux, 7 hr.	81†
Diethyl formamidomalonate	C_2H_5OH, $NaOC_2H_5$, reflux, 5 hr.	81 (88)
Sodium cyanide	$HCON(CH_3)_2$, NaOH, reflux, 3–4 hr.	81 (76)
	$HCON(CH_3)_2$, reflux, 1 hr.	412 (81)

Note: References 382 to 537 are on pp. 266–269.
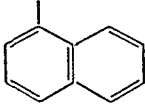
* Monodecarboxylation occurred during amidomethylation. The product isolated was $o\text{-}C_6H_4(CO)_2NCH_2CH(NHCOCH_3)CO_2C_2H_5$.

† The bisamidomethylated derivative was obtained in low yield as the sole product.

TABLE XVI

α-Amidoalkylation of Aliphatic Carbon Atoms with Acylimines

$$C_6H_5CON{=}CAr_2 + HC{\diagdown} \rightarrow C_6H_5CONHC(Ar)_2C{\diagdown}$$
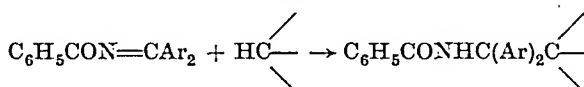
Product Derived from	Method	References (Yield, %)
$C_6H_5CON{=}C(C_6H_5)_2$ and		
Acetonitrile	$LiNH_2$, liq. NH_3	120 (85)
Propionitrile	$LiNH_2$, liq. NH_3	121 (50)
Butyronitrile	$LiNH_2$, liq. NH_3	121 (53)
$C_6H_5CH_2CO_2Na$	i-C_3H_7MgCl, C_6H_6/ether, reflux	19 (49)
$C_6H_5CON{=}C(C_6H_5)C_6H_4OCH_3$-$p$ and		
$C_6H_5CH_2CO_2Na$	i-C_3H_7MgCl, C_6H_6/ether, reflux	19 (53)
$C_6H_5CON{=}C(C_6H_5)$ and		
Acetonitrile	$LiNH_2$, liq. NH_3	120 (59)
Propionitrile	$LiNH_2$, liq. NH_3	121 (36)
Butyronitrile	$LiNH_2$, liq. NH_3	121 (40)*

Note: References 382 to 537 are on pp. 266–269.

* Two diastereoisomers were isolated; one in a 37% and the other in a 3% yield.

TABLE XVII

α-AMIDOALKYLATION OF ETHYL ACETOACETATE WITH N,N'-ALKYLIDENE- AND N,N'-ARYLIDENEBISUREAS ON THEIR PRECURSORS. THE BIGINELLI PYRIMIDINE SYNTHESIS

Method A: $CH_3COCH_2CO_2C_2H_5 + (H_2NCONH)_2CHR \rightarrow$

Method B: $CH_3COCH_2CO_2C_2H_5 + CO(NH_2)_2 + RCHO \rightarrow$

$$O=C \underset{\underset{H}{N}}{\overset{HN}{\bigcirc}} \overset{CH_3}{\underset{CHR}{\overset{C-CO_2C_2H_5}{\Vert}}}$$
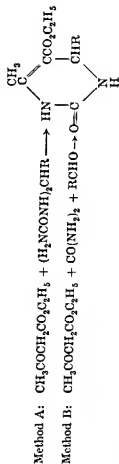
Product Derived from Urea and	Method	References (Yield, %)
Formaldehyde	A; HCl, CH₃CO₂H, 120°	126 (18)
Acetaldehyde	A; 120°, 5-8 hr.	124
	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (26)
	B; HCl, dioxane, 100°, 2 hr.	126 (47)
Heptanal	B; 100°, 2-3 hr.	124
β-Phenylpropionaldehyde	B; HCl, C₂H₅OH, 80°, 5.5 hr.	126 (7)
Cinnamaldehyde	A; C₂H₅OH, 25°, 450 hr.	126 (13)
	B; C₂H₅OH, 80°	123
	B; C₂H₅OH, 80°, 2 hr.	122
	B; CH₃CO₂H, 25°	126 (71)

Note: References 382 to 537 are on pp. 261-269.

TABLE XVII—*Continued*

x-Amidoalkylation of Ethyl Acetoacetate with N,N'-Alkylidene- and N,N'-Arylidene-
bisureas or Their Precursors. The Biginelli Pyrimidine Synthesis

Method A: $CH_3COCH_2CO_2C_2H_5 + (H_2NCONH)_2CHR \longrightarrow$

Method B: $CH_3COCH_2CO_2C_2H_5 + CO(NH_2)_2 + RCHO \rightarrow$

Product Derived from Urea and	Method	References (Yield, %)
Benzaldehyde	A; C₂H₅OH, 80°, 5-6 hr.	122, 125
	B; C₂H₅OH, 80°, 2 hr.	122, 125 (56)
	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (79)
	B; 120°, 6 hr.	125 (60)
	B; CS(NH₂)₂, C₂H₅OH, reflux	125*
m-Nitrobenzaldehyde	B; HCl, C₂H₅OH, 80°, 6 hr.	124, 126 (56)
p-Nitrobenzaldehyde	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (31)
	B; HCl, CH₃CO₂H, 120°, 3 hr.	126 (58)
Salicylaldehyde	A, B; C₂H₅OH, 80°, 2 hr.	122, 123
	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (19)

p-Hydroxybenzaldehyde	B; HCl, C_2H_5OH, 80°, 3 hr.	120 (66)
3,5-Diiodo-4-hydroxybenzaldehyde	B; HCl, CH_3CO_2H, 120°, 2.25 hr.	126 (11)
p-Anisaldehyde	B; HCl, C_2H_5OH, 80°, 3 hr.	126 (61)
2,4-Dihydroxybenzaldehyde	B; CH_3CO_2H, 25°, 120 hr.	126 (34)
Vanillin	B; HCl, C_2H_5OH, 80°, 3 hr.	126 (42)
Veratraldehyde	B; HCl, C_2H_5OH, 80°, 3 hr.	126 (47)
Piperonal	B; HCl, C_2H_5OH, 80°, 3 hr.	126 (49)
2,4,6-Trimethoxybenzaldehyde	B; HCl, C_2H_5OH, 80°, 2 hr.	126 (38)
p-Isopropylbenzaldehyde	A, B; C_2H_5OH, 80°	123
2-Furaldehyde	A; HCl, C_2H_5OH, 80°*	124
	B; C_2H_5OH, 80°, 2 hr.	122, 127, 126 (30)

Note: References 382 to 637 are on pp. 266–299.
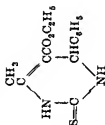
* Thiourea replaced urea to give the corresponding product.

TABLE XVII—*Continued*

α-AMIDOALKYLATION OF ETHYL ACETOACETATE WITH N,N'-ALKYLIDENE- AND N,N'-ARYLIDENE-BISUREAS OR THEIR PRECURSORS. THE BIGINELLI PYRIMIDINE SYNTHESIS

Method A: $CH_3COCH_2CO_2C_2H_5 + (H_2NCONH)_2CHR \longrightarrow$

Method B: $CH_3COCH_2CO_2C_2H_5 + CO(NH_2)_2 + RCHO \rightarrow O=C$

Product Derived from Urea and	Method	References (Yield, %)
Benzaldehyde	A; C₂H₅OH, 80°, 5–6 hr.	122, 125
	B; C₂H₅OH, 80°, 2 hr.	122, 125 (56)
	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (78)
	B; 120°, 6 hr.	125 (60)
	B; CS(NH₂)₂, C₂H₅OH, reflux	125*
m-Nitrobenzaldehyde	B; HCl, C₂H₅OH, 80°, 6 hr.	124, 126 (56)
p-Nitrobenzaldehyde	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (31)
	B; HCl, CF₃CO₂H, 120°, 3 hr.	126 (58)
Salicylaldehyde	A, B; C₂H₅OH, 80°, 2 hr.	122, 123
	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (19)

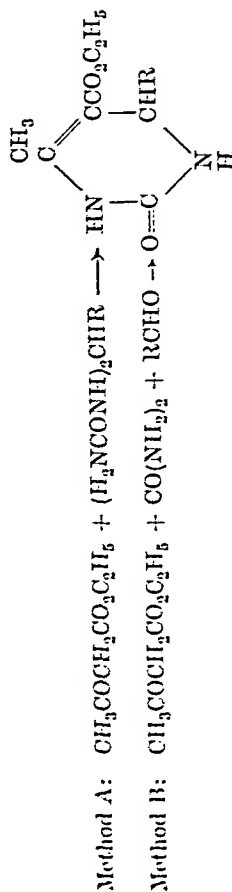|		
p-Hydroxybenzaldehyde	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (66)
3,5-Diiodo-4-hydroxybenzaldehyde	B; HCl, CH₃CO₂H, 120°, 2.25 hr.	126 (11)
p-Anisaldehyde	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (61)
2,4-Dihydroxybenzaldehyde	B; CH₃CO₂H, 25°, 120 hr.	126 (34)
Vanillin	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (42)
Veratraldehyde	B; HCl, C₂H₅OH, 80°, 2 hr.	126 (47)
Piperonal	B; HCl, C₂H₅OH, 80°, 3 hr.	126 (49)
2,4,5-Trimethoxybenzaldehyde	B; HCl, C₂H₅OH, 80°, 2 hr.	126 (38)
p-Isopropylbenzaldehyde	A; B; C₂H₅OH, 80°	123
	A; HCl, C₂H₅OH, 80°	124
2-Furaldehyde	B; C₂H₅OH, 80°, 2 hr.	122, 127, 126 (38)

Note: References 382 to 637 are on pp. 266–290.

* Thiourea replaced urea to give the corresponding product.

TABLE XVIII

x-AMIDOALKYLATION OF ACTIVE METHYLENE COMPOUNDS OTHER THAN ETHYL ACETOACETATE WITH UREA AND ALDEHYDES. THE BIGINELLI PYRIMIDINE SYNTHESIS

$$RCOCH_2COR' + CO(NH_2)_2 + R''CHO \rightarrow$$

Product Derived from Urea	Method	References (Yield, %)
Pentane-2,4-dione and		
Propionaldehyde	HCl, C$_2$H$_5$OH, reflux, 5 hr.	128 (32)
Isovaleraldehyde	HCl, C$_2$H$_5$OH, reflux, 4 hr.	128 (0)
Heptanal	HCl, C$_2$H$_5$OH, reflux, 4 hr.	128 (0)
Cinnamaldehyde	CH$_3$CO$_2$H, 100°, 3 hr.	128 (92)
Benzaldehyde	HCl, C$_2$H$_5$OH, reflux, 3.5 hr.	128 (55)
m-Nitrobenzaldehyde	HCl, C$_2$H$_5$OH, reflux, 3 hr.	128 (70)
Salicylaldehyde	HCl, C$_2$H$_5$OH, reflux, 2 hr.	128 (49)
o-Methoxybenzaldehyde	HCl, C$_2$H$_5$OH, reflux, 3.5 hr.	128 (40)
3,4-Dimethoxybenzaldehyde	HCl, C$_2$H$_5$OH, reflux, 1 hr.	128 (44)
p-(CH$_3$)$_2$NC$_6$H$_4$CHO	HCl, C$_2$H$_5$OH, reflux, 3 hr.	128 (40)
4-Hydroxy-3-methylbenzaldehyde	HCl, C$_2$H$_5$OH, reflux, 3.5 hr.	128 (65)
2-Furaldehyde	CH$_3$CO$_2$H, 100°, 2 hr.	128 (89)

Cyclohexane-1,3-dione and		
n-Butyraldehyde	HCl, C_2H_5OH, reflux, 2.5 hr.	130 (0)
o-Chlorobenzaldehyde	HCl, C_2H_5OH, reflux, 3.5 hr.	130 (80)
p-Methoxybenzaldehyde	HCl, C_2H_5OH, reflux, 3 hr.	130 (0)
p-$(CH_3)_2NC_6H_4CHO$	HCl, C_2H_5OH, reflux, 3 hr.	130 (0)
1-Phenylbutane-1,3-dione and		
Benzaldehyde	HCl, C_2H_5OH, reflux, 3 hr.	129 (51)*
o-Chlorobenzaldehyde	HCl, C_2H_5OH, reflux, 2 hr.	129 (68)*
m-Nitrobenzaldehyde	HCl, C_2H_5OH, reflux, 2 hr.	129 (42)*
p-Hydroxybenzaldehyde	HCl, C_2H_5OH, reflux, 2 hr.	129 (63)*
p-Methoxybenzaldehyde	HCl, C_2H_5OH, reflux, 2 hr.	129 (50)*
Ethyl benzoylacetate and		
Acetaldehyde	HCl, CH_3CO_2H, 100°, 24 hr.	413

Note: References 382 to 537 are on pp. 260–269.

* The relative positions of R and R' in the product were not established.

TABLE XIX

AMIDOMETHYLATION OF POTASSIUM CYANIDE WITH ARENESULFONAMIDOMETHANESULFONATES

$$ArSO_2NHCH_2SO_3Na + KCN \rightarrow ArSO_2NHCH_2CN + NaKSO_3$$
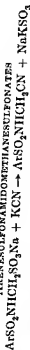
Product Derived from	Method	References (Yield, %)
$C_6H_5SO_2NHCH_2SO_3Na$	H_2O	132
m-$C_6H_4(SO_2NHCH_2SO_3Na)_2$	H_2O	132 (75)

Note: References 382 to 537 are on pp. 260–269.

TABLE XX

N-Monomethylol Derivatives of Carboxamides, Imides, and Sulfonamides

N-Methylol Derivative	Method*	References (Yield, %)
Of Aliphatic Amides		
HCONHCH₂OH	Formalin, base	22
	20% aq. CH₂O, 60°	154
	(CH₂O)x, heat	414
HCON(CH₃)CH₂OH	20% aq. CH₂O, 60°	154
CH₃CONHCH₂OH	Formalin, base	23
	20% aq. CH₂O, 60°	154
	(CH₂O)x, heat	96, 414
	(CH₂O)x, base	217, 415
CH₃CON(CH₃)CH₂OH	20% aq. CH₂O, 60°	154
	(CH₂O)x, 120–145°	32 (good), 244
CH₃CON(C₃H₇-n)CH₂OH	(CH₂O)x, base, 110°	32
CH₃CON(C₃H₇-i)CH₂OH	(CH₂O)x, base, 110°	32
CH₃CON(CH₂C₆H₅)CH₂OH	(CH₂O)x, base, 110°	32
CH₃CON(CH₂NHCOCH₃)CH₂OH	20% aq. CH₂O, 60°	154
CH₃CON(CH₂CH₂NHCOCH₃)CH₂OH	20% aq. CH₂O, 60°	154
CH₃CON(CH₂CH₂CH₂NHCOCH₃)CH₂OH	20% aq. CH₂O, 60°	154
CH₂ClCONHCH₂OH	Formalin, base	11 (100), 52
	Formalin, acid	416
CCl₃CONHCH₂OH	Formalin, base	264 (100)
	Formalin, acid	416
CH₂BrCONHCH₂OH	Formalin, acid	416, 417
CH₂ICONHCH₂OH	Formalin, acid	416, 417
o-CH₃OC₆H₄OCH₂CONHCH₂OH	Formalin, base	418
$\begin{array}{c}\text{OCH}_3\\[4pt]\text{C}_6\text{H}_3\\[2pt]\text{CH}_3\text{CH}\quad\text{CH}\quad\text{OCH}_2\text{CONHCH}_2\text{OH}\end{array}$	RCON(CH₂OH)₂, H₂O	42

CH₂=CHCH₂ [benzene ring with OCH₃]	RCON(CH₂OH)₂, H₂O	42
OCH₂CONHCH₂OH	Formalin, base	79
C₆H₅CH₂CONHCH₂.CONHCH₂OH	Formalin, base	79 (86)
C₆H₅CH₂CONHCH₂.CONHCH₂OH		
NCH₂CONHCH₂OH Cᴼ [benzene ring]	CH₂ClCONHCH₂OH, pyridine	312 (30)
C₆H₅CH₂CONHCH₃	Formalin, base	388 (83)
C₆H₅CH₂CH₂CONHCH₂OH	Formalin, base	43
C₆H₅CH₂CH₂CONHCH₂OH	Formalin, base	163 (90)
CH₃CbCH₂CONHCH₂OH	Formalin, acid	410, 417
CH₃CbCH₂CONHCH₂OH	CH₂=CHCONHCH₂OH, Br₂	253
C₆H₅CH(OH)CONHCH₂OH	Formalin, base	43
C₆H₅CH(CONH₂)CH₂.CONHCH₂OH	Formalin, base	79 (87)
CH₃CO	Formalin, base	79
NCH₂OH	Formalin, base, 85°	177, 184 (85)
CH₂CH₃	(CH₂O)ₓ, 120°	33 (80)
(CH₃)₂CHCONHCH₂OH	Formalin, base	153
(CH₃)₃CHCH₂.CONHCH₂OH	Formalin, base	253 (51)
CH₃CH₂CH.CHCH₂.CONHCH₂OH	Formalin, base	54, 418, 419 (05)
CH₃CH₂CO		
NCH₂OH	Formalin, base, 85°	184 (70)
	(CH₂O)ₓ, base, 140°	310 (67)
CH₃CH₂CF₂	(CH₂O)ₓ, 110°	33
	Formaldehyde	420
(C₆H₅)₂CHCONHCH₂OH	Formalin, base	419 (80)
(n-C₃H₇)₂CHCONHCH₂OH	Formalin, base	153 (82)

* Unless otherwise indicated, the amido or imido is an unnamed reactant.

TABLE XX—*Continued*

N-Monomethylol Derivatives of Carboxamides, Imides, and Sulfonamides

N-Methylol Derivative	Method*	References (Yield, %)
Of Aliphatic Amides (contd.)		
n-$C_{11}H_{23}CONHCH_2OH$	Formalin, base, heat	222 (88)
$CF_3(CH_2)_{11}CONHCH_2OH$	$(CH_2O)_x$, base, C_6H_6, 50°	217 (100)
n-$C_{17}H_{35}CONHCH_2OH$	Formalin, base, 70°	138 (83), 139, 140, 312
	$(CH_2O)_x$, 00°	217 (85)
	$(CH_2O)_x$, heat	139
n-$C_{17}H_{35}CON(CH_3)CH_2OH$	Formalin, base	235
n-$C_{31}H_{63}CONHCH_2OH$	$(CH_2O)_x$, base	254 (70), 421 (87), 422, 423
$CH_3 \cdot CHCONHCH_2OH$	$(CH_2O)_x$, base	312 (91)
o-$CH_2C_6H_4 \cdot CH=\cdot CHCONHCH_2OH$	$(CH_2O)_x$, $NaOC_2H_5$, CCl_4	35 (82)
$C_6H_5 \cdot C(CH_3)CONHCH_2OH$	$(CH_2O)_x$, base	254 (70), 421 (83), 424 (64)
$(CH_3)_3C \cdot CHCONHCH_2OH$	$(CH_2O)_x$, $NaOC_2H_5$, CCl_4	422 (77)
$CH_3 \cdot CH(CH_2)_8CONHCH_2OH$	Formalin, base	382 (96)
$CH_3(CH_2)_2CH \cdot CH(CH_2)_2CONHCH_2OH$	$(CH_2O)_x$, heat	139
$CH_3(CH=\cdot CH)_2CONHCH_2OH$	Formalin, base	389 (78), 423
Of Aromatic Amides		
$C_6H_5CONHCH_2OH$	Formalin, base	1, 10 (100), 52, 79, 88
$C_6H_5CON(CH_3)CH_2OH$	Formalin, acid	263, 425 (64)
$2,4$-$Cl_2C_6H_3CONHCH_2OH$	$(CH_2O)_x$, base, 110°	32
o-$O_2NC_6H_4 \cdot CONHCH_2OH$	Formalin, base	96 (75)
o-$O_2NC_6H_4 \cdot CONHCH_2OH$	Formalin, base	221
m-$O_2NC_6H_4 \cdot CONHCH_2OH$	Formalin, base	221

p-O$_2$NC$_6$H$_4$CONHCH$_2$OH	Formalin, base	221 (56)
o-HOC$_6$H$_4$CONHCH$_2$OH	(CH$_2$O)$_x$, heat	139
p-HOC$_6$H$_4$CONHCH$_2$OH	Formalin, base	25 (93), 418
p-HOC$_6$H$_4$CONHCH$_2$OH	Formalin, acid	25 (92), 425
p-CH$_3$C$_6$H$_4$CONHCH$_2$OH	Formalin, base	418
	Formalin, base	418

Of Heteroaromatic Amides

(furan)-CONHCH$_2$OH	(CH$_2$O)$_x$, base	35
(pyridine)-CONHCH$_2$OH	Formalin, base, heat	426
CH$_3$-(pyridine)N-CONHCH$_2$OH	Formalin, base	426
(pyridine)-CONHCH$_2$OH	Formalin, base	426
Cl-(pyridine)CH$_3$-CONHCH$_2$OH	Formalin, heat	427 (69)
	RCONHCH$_2$OH, CH$_3$Cl	427 (78)
(benzene)CH$_2$SO$_2$O-CONHCH$_2$OH	Formalin, 90°	427 (59)
(benzene)C$_7$H$_{17}$-CONHCH$_2$OH	RCONHCH$_2$OH, C$_8$H$_{17}$OSO$_2$CH$_3$	427 (61)

Note. References 382 to 537 are on pp. 266–269.

° Unless otherwise indicated, the amido or imido is an unnamed reactant.

TABLE XX—*Continued*

N-Monomethylol Derivatives of Carboxamides, Imides, and Sulfonamides

of Heteroaromatic Amides (contd.)

N-Methylol Derivative	Method*	References (Yield, %)
(pyridine) CONHCH₂OH, Br, C₁₂H₂₅-n	RCONHCH₂OH, n-C₁₂H₂₅Br	427 (68)
(pyridine) CONHCH₂OH, Br, C₁₆H₃₃-n	Formalin, 30° RCONHCH₂OH, n-C₁₆H₃₃Br	427 (66) 427 (79)
(pyridine) CONHCH₂OH, Cl, CH₂ClCO₂H	Formalin, 50° RCONHCH₂OH, CH₂ClCO₂H	427 (73) 427
(pyridine) CONHCH₂OH, Cl, CH₂CONH₂	Formalin, 40° RCONHCH₂OH, CH₂ClCONH₂	427 (80) 427 (84)
(pyridine) CONHCH₂OH, CO₂H	Formalin, base, 80°	428
HO₂C—(pyridine)—CONHCH₂OH	Formalin, base, 80°	428 (97)

HO₂C⟶CONHCH₂OH / CH₃⟶ CONHCH₂OH	Formalin, base, 100°	428 (95)
CONHCH₂OH (naphthyl)	Formalin, NaHCO₃, 50° / Formalin, 100°	429 (80) / 430 (60)
CONHCH₂OH (quinolinyl)	Formalin, base, heat	426
OC₄H₉-n, CONHCH₂OH	Formalin, base, heat	426
CONHCH₂OH (quinolinyl)	Formalin, base	242
Of Imides		
CH₂CO⟩NCH₂OH / CH₂CO	Formalin, base	66 (100)
CH₂CO / CHCO⟩NCH₂OH / CH₂CO	N-Methylolmaleimide, HCl	8

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the amide or imido is an unnamed reactant.

TABLE XX—*Continued*
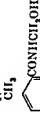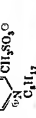
N-Monomethylol Derivatives of Carboxamides, Imides, and Sulfonamides

N-Methylol Derivative	Method*	References (Yield, %)
Of Imides (contd.)		
$C_6H_5CONHCHCO$ ... NCH$_2$OH ... CH$_2$CO	Formalin	431 (92)
CHCO ... NCH$_2$OH ... CHCO	Formalin, base, 35°	8 (75), 432
CO ... NCH$_2$OH ... CO (with CH$_2$)		433
o-C$_6$H$_4$(CO)$_2$NCH$_2$OH	Formalin, heat	1, 84 (90), 434, 435 (90)
	10–15% aq. CH$_2$O, heat	104 (excellent)
NO$_2$ ... CO ... NCH$_2$OH ... CO	Formalin, 100°	436
O$_2$N ... CO ... NCH$_2$OH ... CO	Formalin, 100°	436
SO$_2$ ... NCH$_2$OH ... CO	Formalin, 100° / Formalin, heat	99 (69) / 182 (81), 437

o-$C_6H_4(CO_2N)$SO$_2$NCH$_2$OH, CH$_3$CO	Formalin, base	157
o-$C_6H_4(CO_2N)$SO$_2$NCH$_2$OH	Formalin, base	157
($C_2H_5)_2$NCH$_2$CO		
Of Sulfonamides		
C_6H_5SO$_2$NHCH$_2$OH	Formalin, base	155 (60), 156
p-CH$_3C_6H_4$SO$_2$NHCH$_2$OH	Formalin, base	155 (93), 156 (60), 438
o-$C_6H_4(CO_2N)$SO$_2$N (CH$_2$OH)	Formalin, base	157
o-$C_6H_4(CO_2N)$SO$_2$N (CH$_2$OH)	Formalin, base	157

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the amido or imido is an unnamed reactant.

TABLE XX—*Continued*

N-Monomethylol Derivatives of Carboxamides, Imides, and Sulfonamides

N-Methylol Derivatives	Method*	References (Yield, %)
Of Sulfonamides (contd.)		
o-C₆H₄(CO)₂N— structure (thiazole, CH₂OH)	Formalin, base	157
o-C₆H₄(CO)₂N— structure (thiazole, C₂H₅, CH₂OH)	Formalin, base	157
o-C₆H₄(CO)₂N— structure (pyrimidine, CH₃, CH₂OH)	Formalin, base	157
o-C₆H₄(CO)₂N— structure (pyrimidine, CH₃, CH₃, CH₂OH)	Formalin, base	157

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the amido or imido is an unnamed reactant.

TABLE XXI

POLY-N-METHYLOL DERIVATIVES OF MONO- AND POLY-CARBOXAMIDES

N-Methylol Derivatives	Method*	References (Yield, %)
Of Monocarboxamides		
[structure] $CON(CH_2OH)_2$	Formalin, base	41 (100)
$CH_2CH=CH$ OCH_3 $OCH_2CON(CH_2OH)_2$	Formalin, base	42
$CH_2=CHCH_2$ OCH_3 $OCH_2CON(CH_2OH)_2$	Formalin, base	42
Of Polycarboxamides		
$(CON(CH_2OH)_2$	Formalin, base	35 (47)
$(C_2H_4)_3CONHCH_2OH)_2$	Formalin, base	263 (100)
$(CH_2)_4(CONHCH_2OH)_2$	Formalin, base	24 (80)
$CHOHCONHCH_2OH$		
$CHOHCONHCH_2OH$	Formalin, base	43 (70)
$(CH_2)_4(CONHCH_2OH)_2$	Formalin, base	406 (71)
$(CH_2)_4(CONHCH_2OH)_2$	Formalin, base	406 (50)
$(CH_2)_5(CONHCH_2OH)_2$	Formalin, base	406 (60)

Note: References 382 to 537 are on pp. 206–260.
* The amide is an unnamed reactant.

TABLE XXI—*Continued*

POLY-N-METHYLOL DERIVATIVES OF MONO- AND POLY-CARBOXAMIDES

N-Methylol Derivatives	Method*	References (Yield, %)
Of Polycarboxamides (contd.)		
$(CH_2)_4(CONHCH_2OH)_2$	Formalin, base	406 (81)
$CH_2CONHCH_2OH$		
$HOCCONHCH_2OH$	Formalin, base	43 (20)
$CH_2CONHCH_2OH$		
$HOCH_2N$ (ring) NCH_2OH	Formalin	1, 65 (90)
	Formalin, base	79
	Formalin, acid	79 (0)
$CH_2N(CHO)CH_2OH]_2$	20% aq. CH_2O, 60°	154
$[CH_2N(CHO)CH_2OH]_2$	20% aq. CH_2O, 60°	154
$CH_3CHN(CHO)CH_2OH$	20% aq. CH_2O, 60°	154
$CH_2N(CHO)CH_2OH$	20% aq. CH_2O, 60°	154
$CH_2[CH_2N(CHO)CH_2OH]_2$	20% aq. CH_2O, 60°	154
$HOCH[CH_2N(CHO)CH_2OH]_2$	20% aq. CH_2O, 60°	154

HCONHCH₂CH₂N(CH₂OH)₂	20% aq. CH₂O, 60°	154
HCCONHCH₂OH		
HCONHCH₂OH	Formalin, acid	423
HOCH₂NHCOCH		
HCCONHCH₂OH	Formalin, base	254 (53)
OCH₂CONHCH₂OH	Formalin, base	254 (49)
OCH₂CONHCH₂OH		
OCl₂CONHCH₂OH	Formalin, base	439
OCH₂CONHCH₂OH		
HOCH₂NHCO⟨pyridine⟩CONHCH₂OH	Formalin, base	439
HOCH₂NHCO⟨pyridine⟩CONHCH₂OH / CH₃	Formalin, base 100°	428 (50)
	Formalin, NaHCO₃, 100°	428

CH_3
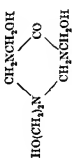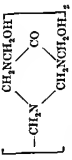
Note: References 382 to 537 are on pp. 266–269.

* The amido is an unnamed reactant.

TABLE XXII

N-Mono- and N,N-Di-methylol Derivatives of Carbamyl Compounds

N-Methylol Derivatives	Method*	References (Yield, %)
$C_7H_5O_2CNHCH_2OH$	Formalin, acid	153 (60)
$n\text{-}C_{23}H_{45}O_2CNHCH_2OH$	$(CH_2O)_x$, pyridine, 90°	235
$C_6H_5CH_2NHCOCH_2NCH_2OH$ $CO_2CH_2C_6H_5$	$C_6H_5CH_2O_2CN\big\langle\begin{smallmatrix}CH_2CO\\ \ \ \ CH_2\end{smallmatrix}\big\rangle O$, $C_6H_5CH_2NH_2$	344 (91)
$H_2NCONHCH_2OH$	Formalin, base	153, 440–443
	Formalin, pH 8.5	144 (20)
	$(CH_2O)_x$, base	444
$CO(NHCH_2OH)_2$	Formalin, base	153, 442, 445 (90)
	$(CH_2O)_x$, base, 15°	444 (100), 446
	Formalin	440, 443
$O(CH_2NHCONHCH_2OH)_2$	$CO(NHCH_2OH)_2$, base	62
$CH_3NHCON(CH_3)CH_2OH$	Formalin, base	153 (71)
$(CH_3)_2NCONHCH_2OH$	Formalin, base	153 (75)
$C_6H_5NHCONHCH_2OH$	$(CH_2O)_x$, base	54, 55, 62
$p\text{-}CH_3C_6H_4NHCONHCH_2OH$	$(CH_2O)_x$, base	55
$H_2NCONHCH_2NHCONHCH_2OH$	Formalin, base	219 (10)
$CH_2(NHCONHCH_2OH)_2$	Formalin, base	219 (20)
$H_2N(CSNHCH_2OH$	Formalin, base	265 (96)
$CS(NHCH_2OH)_2$	Formalin, base	265 (100)

Structure	Reactant	Reference
CH₂NCH₂OH CO CH₂NCH₂OH	Formalin, base	447 (60), 448, 449, 450 (66)
CH₂NCH₂OH CO C₄H₂N—CH₂NCH₂OH	Formalin, base, 70°	451 (97) 452a
HO(CH₂)ₙN—CH₂NCH₂OH CO CH₂NCH₂OH	Formalin	452a
[CH₂NCH₂OH CO CH₂N—CH₂NCH₂OH₂]—CH₂—	Formalin	452a
CONCH₂OH CO CH₂NH	Formalin, heat	185 (76)

Note: References 382 to 537 are on pp. 268–269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—*Continued*

N-Mono- and N,N'-Di-methylol Derivatives of Carbamyl Compounds

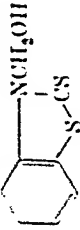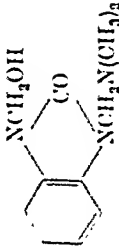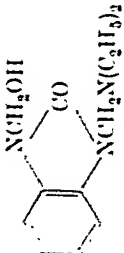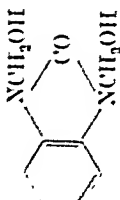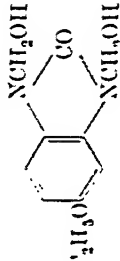| N-Methylol Derivatives	Method*	References (Yield, %)
$\begin{array}{c}\text{CONCH}_2\text{OH}\\ | \quad\backslash\\ \text{(CH}_3)_2\text{CNH}\!-\!\text{CO}\end{array}$	Formalin, heat	453 (99)
$\begin{array}{c}\text{CONCH}_2\text{OH}\\ | \quad\backslash\\ \text{C}_6\text{H}_5\text{CHNH}\!-\!\text{CO}\end{array}$	Formalin, heat	187 (92)
$\begin{array}{c}\text{OC}\!-\!\text{NCH}_2\text{OH}\\ | \quad\quad\backslash\\ \text{C}_6\text{H}_5\text{C(CH}_3)\text{NH}\!-\!\text{CO}\end{array}$	Formalin, heat	187 (96)
$\begin{array}{c}\text{OC}\!-\!\text{NCH}_2\text{OH}\\ | \quad\quad\backslash\\ \text{C}_6\text{H}_5(\text{C}_2\text{H}_5)\text{NH}\!-\!\text{CO}\end{array}$	Formalin, heat	187 (97)
$\begin{array}{c}\text{C}\!-\!\text{NCH}_2\text{OH}\\ \text{CONCH}_2\text{OH}\quad\backslash\\ \text{CH}_2\text{NCH}_3\end{array}$	Formalin, creatine Formalin, creatinine	454 (90) 454 (80)

Structure	Reagent	Yield
CHNCH$_2$OH / CS / CHNCH$_3$	Formalin, base	455 (72)
CHCO / CH$_3$C—NCH$_2$OH / NHCS	Formalin, heat	239
CHCO / n-C$_3$H$_7$C—NCH$_2$OH / NHCS	Formalin, heat	239
—NCH$_2$OH —CO—O—	Formalin, 100°	194 (82)
—NCH$_2$OH —CS—O— (DL-trans)	Formalin, heat	181 (75)
—NCH$_2$OH —CS—O—	Formalin, 100°	178 (70)

Note: References 382 to 537 are on pp. 260–269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—*Continued*

N-Mono- and N,N'-Di-methylol Derivatives of Carbamyl Compounds
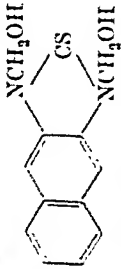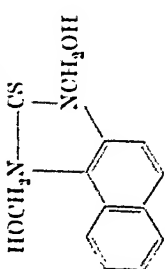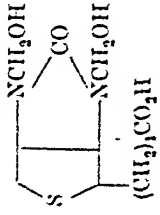
N-Methylol Derivatives	Method*	References (Yield, %)
(structure: benzo ring with NCH₂OH and CS, S)	Formalin, heat	183 (96), 189 (84)
(structure: benzo ring with NCH₂OH, CO, NCH₂N(CH₃)₂)	Formalin, (CH₃)₂NH	180·(54)
(structure: benzo ring with NCH₂OH, CO, NCH₂N(C₂H₅)₂)	Formalin, (C₂H₅)₂NH	180 (30)
(structure: benzo ring with NCH₂OH, CO, NCH₂OH)	Formalin, 100°	180 (80), 238, 456
(structure: benzo ring with C₂H₅O, NCH₂OH, CO, NCH₂OH)	Formalin, 100°	237

Formalin, heat		456 (71)
Formalin, base		457 (77)
Formalin, 100°		179 (83), 238
Formalin, 100°		237
Formalin, 100°		239

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—*Continued*

N-Mono- and N,N′-Di-methylol Derivatives of Carbamyl Compounds

N-Methylol Derivatives	Method*	References (Yield, %)
(naphthalene ring with NCH₂OH, CS, NCH₂OH)		239, 457
(naphthalene ring with HOCH₂N—CS, NCH₂OH)	Formalin, 100°	241
(ring with NCH₂OH, CO, NCH₂OH, S)	$(CH_2O)_x$, base, 50°	458 (45)
$(CH_2)_4CO_2H$		

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXIII

α-Hydroxyalkyl Derivatives of Carboxamides, Carbamyl Compounds, and Sulfonamides

$$RCONH_2 + RCHO \rightarrow RCONHCHOHR'$$

(R'=alkyl)

α-Alkylolamide Derivative	References (Yield, %)	α-Alkylolamide Derivative	References (Yield, %)	α-Alkylolamide Derivative	References (Yield, %)
Of Aliphatic Monoamides					
HCONHCHOHCCl₃	95, (100), 459	CH₃CO \		CH₃CH₂ \ CHOHCCl₃	101 (60), 467
HCONHCHOHCH₂CCl₃	207	NCHOHCCl₃			
C₂H₅CONHCHOHCCl₃	403	CH₃CH /			
CH₃CONHCHOHCCl₃	100, 163, 229				
CH₃CONHCHOHC₆H₅	208				
CH₃CONHCHOHCH₃	95, 158, 460 (50), 461, 462	n-C₃H₇CONHCHOHCCl₃		n-C₄H₉CONHCHOHCHClCH₂CH₃	164, 460 (78)
CH₃CONHCHOHCH₂CH₃	460, 463 (70), 464	n-C₄H₉CONHCHOHCCl₃		n-C₆H₁₃CONHCHOHCHClCH₂CH₃	460 (69)
CH₃CONHCHOHCCl₃	464	i-C₃H₇CONHCHOHCCl₃		i-C₃H₇CONHCHOHCHClCH₂CH₃	460 (41)
CH₃CHCONHCHOHCCl₃·CH₂CH₃	460 (43), 466	(CH₃)₂CHCH₂CONHCHOHCCl₃		n-C₃H₇CONHCHOHCHClCH₂CH₃	207
	460 (43)	n-C₆H₁₃CONHCHOHCCl₃		(CH₃)₂CHCONHCHOHCHClCH₂CH₃	460 (14)
CH₃CONHCHOHCCl₃	164, 460 (77)	n-C₇H₁₅CONHCHOHCCl₃		n-C₇H₁₅CONHCHOHCCl₃	403
C₂H₅CONHCHOHCCl₃	166	i-C₃H₇CONHCHOHCCl₃		C₆H₅CH₂CONHCHOHCCl₃	164, 460 (69)
C₆H₅CH₂CONHCHOHCCl₃	460 (37)	(C₆H₅)₂CHCONHCHOHCCl₃		(C₆H₅)₂CHCONHCHOHCCl₃	207
NCOCH₂CONHCHOHCCl₃	166	n-C₃H₇CONHCHOHCHClCH₂CH₃		n-C₃H₇CONHCHOHCHClCH₂CH₃	460 (62)
n-C₃H₇CONHCHOHCCl₃	163	n-C₄H₉CONHCHOHCHClCH₂CH₃		n-C₄H₉CONHCHOHCHClCH₂CH₃	460 (78)
n-C₄H₉CONHCHOHCCl₃	208	n-C₅H₁₁CONHCHOHCCl₃		n-C₅H₁₁CONHCHOHCCl₃	460 (42)
n-C₅H₁₁CONHCHOHCCl₃	184, 460 (76)	n-C₆H₁₃CONHCHOHCCl₃		n-C₆H₁₃CONHCHOHCCl₃	460 (78)
n-C₆H₁₃CONHCHOHCCl₃	207	i-C₃H₇CONHCHOHCCl₃		n-C₇H₁₅CONHCHOHCCl₃	207
				i-C₃H₇CONHCHOHCH₂CCl₃	164, 460 (81)
n-C₃H₇CONHCHOHCCl₃	460 (95)			n-C₃H₇CONHCHOHCCl₃	460 (72)
i-C₃H₇CONHCHOHCCl₃	460 (70)			n-C₄H₉CONHCHOHCBr₃	460 (100)
n-C₄H₉CONHCHOHCCl₃	156			n-C₅H₁₁CONHCHOHCCl₃	207
i-C₄H₉CONHCHOHCCl₃	460 (66)			n-C₆H₁₃CONHCHOHCCl₃	460 (68)
i-C₃H₇CH₂CH₂CONHCHOHCCl₃	460 (38)			n-C₇H₁₅CONHCHOHCCl₃	460 (98)
i-C₄H₉CONHCHOHCCl₃	184			n-C₅H₁₁CONHCHOHCCl₃	460 (76)
i-C₅H₁₁CONHCHOHCCl₃	207			i-C₄H₉CONHCHOHCCl₃	460 (57)
n-C₆H₁₃CONHCHOHCH₂CONHCH₃	466 (75)			i-C₅H₁₁CONHCHOHCCl₃	460 (39)
				n-C₆H₁₃CONHCHOHCCl₃	207
				n-C₇H₁₅CONHCHOHCH₂CH₂CH₃	460 (43)

Note. Reference 382 to 537 are on Pp. 266–269.

* This substance was prepared by an indirect method.
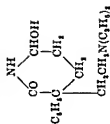
TABLE XXIII—*Continued*

α-Hydroxyalkyl Derivatives of Carboxamides, Carbamyl Compounds, and Sulfonamides

$RCONH_2 + R'CHO \rightarrow RCONHCHOHR'$

(R''=haloalkyl)

α-Alkylolamide Derivative	References (Yield, %)	α-Alkylolamido Derivative	References (Yield, %)
Of Aliphatic Monoamides (contd.)		2-HO-5-Br-3-O₂NC₆H₂CONHCHOHCCl₃	169 (99)
$n\text{-}C_3H_7CONHCHOHCCl_3$	169	2-HO-3,5-(O₂N)₂C₆H₃CONHCHOHCCl₃	169 (85)
$CH_3\cdot CHCONHCHOHCCl_3$	101 (60)	2-HO-5-Cl₃CONHCₑHₑCONHCHOHCCl₃	372 (98)
		o-CH₃OC₆H₄CONHCHOHCCl₃	166, 171 (good)
		m-CH₃OC₆H₄CONHCHOHCCl₃	171 (good)
CH CHCHCONHCHOHCCl₃	204 (30)	p-CH₃OC₆H₄CONHCHOHCCl₃	171 (good)
OC————NCHOHCCl₃		2-CH₃O-3-ClC₆H₃CONHCHOHCCl₃	171 (82)
		2-CH₃O-5-ClC₆H₃CONHCHOHCCl₃	171 (79)
Cl_3CCH CHCCl₃	172	2-CH₃O-3,5-Cl₂C₆H₃CONHCHOHCCl₃	171 (79)
O		2-CH₃O-2-BrC₆H₃CONHCHOHCCl₃	169
		2-CH₃O-3,5-Br₂C₆H₂CONHCHOHCCl₃	169
		2-CH₃O-3,5-(O₂N)₂C₆H₂CONHCHOHCCl₃	169
		2-CH₃O-5-O₂NC₆H₃CONHCHOHCCl₃	169
		o-CH₃CO₂C₆H₄CONHCHOHCCl₃	364
Of Aromatic Amides		m-CH₃CONHC₆H₄CONHCHOHCCl₃	170 (90)
$C_6H_5CONHCHOHCCl_3$ *	208	m-CH₃CONHC₆H₄CONHCHOHCCl₃	170 (85)
$C_6H_5CONHCHOHCHBr_2$ *	208	p-CH₃CONHC₆H₄CONHCHOHCCl₃	170 (90)
$C_6H_5CONHCHOHCCl_3$	95, 171 158, 47	2-CH₃CONH-5-BrC₆H₃CONHCHOHCCl₃	170 (85)
$C_6H_5CONHCHOHCBrCl_2$ *	208	o-C₆H₅CONHC₆H₄CONHCHOHCCl₃	170
$C_6H_5CONHCHOHCBr_2$	106, 208	m-C₆H₅CONHC₆H₄CONHCHOHCCl₃	170 (90)
$C_6H_5CONHCHOHCCl_2CHClCH_3$	463, 464	p-C₆H₅CONHC₆H₄CONHCHOHCCl₃	170 (90)
o-HOC₆H₄CONHCHOHCCl₃	364	2-C₆H₅CONH-5-BrC₆H₃CONHCHOHCCl₃	170 (75)
o-HOC₆H₄CONHCHOHCBr₃	169	o-CH₃C₆H₄CONHCHOHCCl₃	108
m-HOC₆H₄CONHCHOHCCl₃	169	m-CH₃C₆H₄CONHCHOHCCl₃	108
p-HOC₆H₄CONHCHOHCCl₃	170 (0)	p-CH₃C₆H₄CONHCHOHCCl₃	166, 168
2-HO-3-ClC₆H₃CONHCHOHCCl₃	171 (0)		
2-HO-5-ClC₆H₃CONHCHOHCCl₃	171 (81), 470a		
2-HO-3,5-Cl₂C₆H₂CONHCHOHCCl₃	171 (55)		165
2-HO-3-BrC₆H₃CONHCHOHCCl₃	171 (82)		
2-HO-5-BrC₆H₃CONHCHOHCCl₃	169		
2-HO-3,5-Br₂C₆H₂CONHCHOHCCl₃	169		
2-HO-3-O₂NC₆H₃CONHCHOHCCl₃	169		
	169 (77)		

Of Heteroaromatic Amides

[furyl]CONHCHOHCCl₃	204 (86)
Br[furyl]CONHCHOHCCl₃	204 (84)
O₂N[furyl]CONHCHOHCCl₃	204 (64)
CH₃[furyl]CONHCHOHCCl₃	204 (74)
(Cl₃)[furyl]CONHCHOHCCl₃	204 (91)
[pyridyl]CONHCHOHCCl₃	471

Of Lactams

	174
	174 (30)
	175 (86)
	175 (50)
	175 (23)

Of Dicarboxamides

(CONHCHOHCCl₃)₂	163 (31)
C₂H₄(CONHCHOHCCl₃)₂	163
[CH₂CONHCHOHCCl₃]₂	106
C₃H₆(CONHCHOHCCl₃)₂	163
[CH₂CH₂CONHCHOHCCl₃]₂	281
C₄H₈[CH₂CONHCHOHCCl₃]₂	163
C₆H₄(CONHCHOHCCl₃)₂	163
C₆H₄[CH₂CONHCHOHCCl₃]₂	163
C₆H₄[SiH(CH₃)CONHCHOHCCl₃]₂	103
C₆H₄[CH₂CONHCHOHCCl₃]₂	103
(CH₃)₂CONHCHOHCCl₃)₂	106

Note   References 382 to 637 are on pp. 266–299.
* This substance was prepared by an indirect method.

TABLE XXIII—*Continued*

α-Hydroxyalkyl Derivatives of Carboxamides, Carbamyl Compounds, and Sulfonamides

$$RCONH_2 + R'CHO \rightarrow RCONHCHOHR'$$

(R' = haloalkyl)

α-Alkylolamide Derivative	References (Yield, %)	α-Alkylolamide Derivative	References (Yield, %)
Of Lactams (contd.)			
CHOH/CO >NC₆H₄NO₂-p	175 (81)	(quinoline/cyclohexane structure) CH₃O, CH₃O, HO, N=O	472
CHOH/CO >NC₆H₄OCH₃-o	175 (27)	*Of Carbamyl Compounds*	
CHOH/CO >NC₆H₄OCH₃-p	175 (18)	$CH_3O_2CNHCHOHCCl_3$	95 (100), 107
		$C_2H_5O_2CNHCHOHCCl_3$	94 (100), 95, 107, 173, 229
		$C_2H_5O_2CNHCHOHCBr_3$	173
		$C_2H_5O_2CNHCHOHCCl_2CHClCH_3$	173
CHOH/CO >NC₆H₄CH₃-o	175 (23)	$C_2H_5O_2CNHC(OH)(CF_2Cl)_3$	73
		$n\text{-}C_3H_7O_2CNHCHOHCCl_3$	107 (90)
		$i\text{-}C_3H_7O_2CNHCHOHCCl_3$	107
CHOH/CO >NC₆H₄CH₃-p	175 (40)	$i\text{-}C_4H_9O_2CNHCHOHCCl_3$	95
		$Menthyl\text{-}O_2CNHCHOHCCl_3$	100
		$Bornyl\text{-}O_2CNHCHOHCCl_3$	158, 161, 162, 473 (90)
		$H_2NCONHCHOHCCl_3$	73, 158, 160, 161, 162, 473 (71)
(naphthalene structure) CHOH/CO >N	175 (37)	$CO(NHCHOHCCl_3)_2$	
		(structure) NHCHOHCCl₃ / CO, NHCHOHCBr₃, NHCHOHCCl₃	162, 474
(complex alkaloid structure) HO, HO, CH₃O, N, O	472	(structure) NHCH(OCH₃)₂CCl₃ / CO	161

Of Carbonyl Compounds (contd.)

C₂H₅NHCONHCHOHCCl₃	73, 161 (83)
C₂H₅NHCONHCHOHCBr₃	163
p-ClC₆H₄NHCONHCHOHCCl₃	73
m-O₂NC₆H₄NHCONHCHOHCCl₃	227
o-O₂NC₆H₄NHCONHCHOHCCl₃	227
o-CH₃C₆H₄NHCONHCHOHCCl₃	163
o-CH₃OC₆H₄NHCONHCHOHCCl₃	163
(C₂H₅)₂NCONHCHOHCCl₃	160
CS(NHCHOHCCl₃)₂	160
CCl₃CH=NC(=S)NHCHOHCCl₃	160

NHCHOHCCl₃		
CO		161
NHCO(C₂H₄)₂CCl₃		

NHCHOHCCl₃		
CO		161
NHCO(C₄H₉-n)CCl₃		

$$\begin{array}{c} N \quad CHOH \\ \diagdown \quad CO \\ \diagup \quad NH \end{array}$$ 176 (80)

NHCHOHCCl₃		
CO		162
NHCO(C₂H₄)₂CH₃		

Of Sulfonamides

C₂H₅CH₂SO₂NHCHOHCCl₃	159
C₄H₉SO₂NHCHOHCCl₃	159
p-ClC₆H₄SO₂NHCHOHCCl₃	159
p-O₂NC₆H₄SO₂NHCHOHCCl₃	159
p-CH₃C₆H₄SO₂NHCHOHCCl₃	159
m-CH₃C₆H₄SO₂NHCHOHCCl₃	159
p-CH₃OC₆H₄SO₂NHCHOHCCl₃	159
2,4,6-(CH₃)₃C₆H₂SO₂NHCHOHCCl₃	159

CH₃SHCON(CHOHCCl₃)₂	475
CH₃SHCH(OHCCl₃)	163
(C₂H₅)₂NCSNHCHOHCCl₃	163
(C₂H₅)₂NCSNHCHOHCCl₃	163
(C₂H₅)₂NCSNHCHOHCBr₃	163
(C₂H₅)₂NCSNHCHOHCCl₃	163
CCl₃CH₂SO₂NHCHOHCCl₃CH₂F	73

naphthalene-SO₂NHCHOHCCl₃   159

TABLE XXIV

ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
Amides			
HCONHCH$_2$OCH$_3$	415 (11)	(n-C$_{11}$H$_{23}$CONHCH$_2$)$_2$O	217 (70), 222
HCON(CH$_3$)CH$_2$O	470 (>64)	n-C$_7$H$_{15}$CONHCH$_2$OCH$_3$	138 (85), 217, 478
CH$_3$CONHCH$_2$OCH$_3$	415 (90–94)	n-C$_7$H$_{15}$CONHCH$_2$OC$_2$H$_5$	138 (84), 217
CH$_3$CHCONHCH$_2$OCH$_2$C$_4$H$_9$	312	n-C$_7$H$_{15}$CONHCH$_2$OC$_3$H$_7$,n	217 (70)
C$_2$H$_5$CH(CONHCH$_2$CONHCH$_2$OCH$_3$	70	n-C$_7$H$_{15}$CONHCH$_2$OC$_3$H$_7$,i	138 (85), 217
C$_2$H$_5$CH(CONHCH$_2$CONHCH$_2$OC$_2$H$_5$	70	n-C$_7$H$_{15}$CONHCH$_2$OC$_4$H$_9$,n	138, 217
C$_2$H$_5$CH$_2$CONHCH$_2$CONHCH$_2$OC$_2$H$_5$	70	n-C$_7$H$_{15}$CONHCH$_2$OC$_6$H$_{11}$,n	138 (50), 478, 479
C$_2$H$_5$CH$_2$CONHCH$_2$CONHCH$_2$OCH$_2$C$_4$H$_3$	70	n-C$_7$H$_{15}$CONHCH$_2$OC$_8$H$_{17}$	478
C$_2$H$_5$CH$_2$CONHCH$_2$CONHCH$_2$OCH$_2$CHCOC$_2$H$_5$	70 (27)	n-C$_7$H$_{15}$CONHCH$_2$OCH$_2$C$_6$H$_5$	138 (50), 217
		n-C$_7$H$_{15}$CONHCH$_2$OC$_6$H$_5$	217 (95)
NHCOC$_6$H$_5$		(n-C$_7$H$_{15}$CONHCH$_2$)$_2$O	479
C$_2$H$_5$CH$_2$CONHCH$_2$OCH$_3$	70	n-C$_7$H$_{15}$CONHCH$_2$OCH$_2$CO$_2$H	479
C$_2$H$_5$CH$_2$CONHCH$_2$OC$_2$H$_5$	70	n-C$_7$H$_{15}$CONHCH$_2$OCH(CH$_3$)CO$_2$H	479
C$_2$H$_5$CH$_2$CONHCH$_2$OCH$_2$C$_4$H$_9$	79	n-C$_2$H$_5$CH$_2$CONHCH$_2$OCH$_2$PO(OH)$_2$	235
		n-C$_8$H$_{17}$CONHCH$_2$OC$_2$H$_5$	217 (90)
⟨benzene⟩NCH$_2$CONHCH$_2$OCH$_3$C$_6$H$_5$ Cl⊖	312	(n-C$_{11}$H$_{23}$CONHCH$_2$)$_2$O	423 (70), 477, 480
C$_2$H$_5$CH$_2$CONHCH$_2$OC$_2$H$_5$	70	CH$_2$=CHCONHCH$_2$OCH$_3$	477
C$_2$H$_5$CH$_2$CONHCH$_2$OC$_2$H$_5$,n	79	(CH$_2$=CHCONHCH$_2$)$_2$O	422 (55)
C$_6$H$_5$CH$_2$CONHCH$_2$OCH$_3$C$_2$H$_5$	388 (73)	CH$_2$=C(CH$_3$)CONHCH$_2$OCH$_3$	477 (90),
C$_6$H$_5$CH$_2$CONHCH$_2$OCH$_2$CHCO$_2$C$_2$H$_5$	70	CH$_2$=C(CH$_3$)CONHCH$_2$OCH$_3$	480 (80)
		CH$_2$=C(CH$_3$)CONHCH$_2$OC$_2$H$_5$	477
NHCOC$_6$H$_5$		CH$_2$=C(CH$_3$)CONHCH$_2$OC$_3$H$_7$	477
(C$_2$H$_5$CONHCH$_2$)$_2$O	153 (55)	CH$_2$=C(CH$_3$)CONHCH$_2$OCH(CH$_2$Cl)$_2$	477
C$_2$H$_5$CH$_2$CONHCH(CH$_3$)CONHCH$_2$OC$_2$H$_5$	70	CH$_2$=C(CH$_3$)CONHCH$_2$OC$_4$H$_9$	477
C$_2$H$_5$CH$_2$CONHCH(CH$_3$)CONHCH$_2$OCH$_2$C$_4$H$_9$	70	CH$_2$=C(CH$_3$)CONHCH$_2$OC$_6$H$_{13}$	477
(i-C$_4$H$_9$CONHCH$_2$)$_2$O	54	CH$_2$=C(CH$_3$)CONHCH$_2$OC$_{12}$H$_{25}$	477
		CH$_2$=C(CH$_3$)CONHCH$_2$OC$_{18}$H$_{37}$	477

Amides (contd.)

CH₂=C(CH₃)CONHCH₂O—		477	
CH₂=C(CH₃)CONHCH₂OCH₃,CH₂—CH₃		477	
CH₂=C(CH₃)CONHCH₂OC₂H₅-n		477	
CH₂=C(CH₃)CONHCH₂O—		424 (13)	
CH₃CH₂CH₂CONHCH₂OCH₃		423 (64), 480	
CH₃CH₂CH₂CONHCH₂O—		312	
CICH₂CONHCH₂OCH₃			
CICH₂CONHCH₂OC₂H₅-n		423	
C₂H₅CONHCH₂OCH₃		79	
C₂H₅CONHCH₂OC₂H₅-n		478, 479	
C₂H₅CONHCH₂OC₄H₉-t		96 (54)	
(C₂H₅)₂CHCONHCH₂O—		10, 14 (80),	
		220 (77)	
(o-O₂NC₆H₄CONHCH₂)₂O		221 (50)	
		430 (43)	

Lactams

	481 (64)	
	33 (77), 481 (59)	
	481 (68)	
	481 (39)	
	65 (86)	
	85	

CONHCH₂OCH₃	430	
CONHCH₂OC₂H₅-n	430	
CONHCH₂OC₂H₅-n	430	
CONHCH₂OC₄H₉-t	420	
CONHCH₂OC₆H₅	430	

TABLE XXIV—*Continued*

ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
Imides		$o\text{-}C_6H_4(CO)_2NCH_2OC_{14}H_{29}\text{-}n$	71 (83)
$\mathrm{CH_3CO}{>}NCH_2OCH_3$	188	$o\text{-}C_6H_4(CO)_2NCH_2OC_{16}H_{33}\text{-}n$	71 (66)
		$o\text{-}C_6H_4(CO)_2NCH_2OC_{18}H_{37}\text{-}n$	71 (97)
		$o\text{-}C_6H_4(CO)_2NCH_2OC_6H_{11}\text{-}cyclo$	71 (94)
		$o\text{-}C_6H_4(CO)_2NCH_2OCH_2CH_2C_6H_5$	71 (86)
		$o\text{-}C_6H_4(CO)_2NCH_2OCH_2CH(C_6H_5)_2$	71 (65)
		$o\text{-}C_6H_4(CO)_2NCH_2OC(C_6H_5)_3$	71 (50)
$\mathrm{CH_3CO}{>}NCH_2OC_2H_5$	60	$o\text{-}C_6H_4(CO)_2NCH_3OCH_2$	71 (50)
		$o\text{-}C_6H_4(CO)_2NCH_2OCHCH_3$	70
		$o\text{-}C_6H_4(CO)_2NCH_3OCH_2$—	
$[\mathrm{CH_3CO}{>}NCH_2 \,\,O]_2$	85 (17)	$o\text{-}C_6H_4(CO)_2NCH_3OCH_3$	61, 151, 220, 263
		$[o\text{-}C_6H_4(CO)_2NCH_2]_2O$	70
$[\mathrm{CHCO}{>}NCH_2 \,\,O]_2$	8 (41)	*Carbamyl Compounds*	
		$C_2H_5O_2CNHCH_2OCH_3$	218 (95)
$o\text{-}C_6H_4(CO)_2NCH_2OCH_3$	70, 71, 151, 188	$C_2H_5O_2CNHCH_2OC_2H_5$	218 (82)
		$C_2H_5O_2CNHCH_2OC_3H_7\text{-}n$	218 (96)
$o\text{-}C_6H_4(CO)_2NCH_2OC_2H_5$	70, 71 (92), 104 (good), 151	$(C_2H_5O_2CNHCH_2)_2O$	153, 218
		$n\text{-}C_{18}H_{37}O_2CNHCH_2OCH_2CO_2H$	479
$o\text{-}C_6H_4(CO)_2NCH_2OC_3H_7\text{-}n$	70		
$o\text{-}C_6H_4(CO)_2NCH_2OC_3H_7\text{-}i$	70	$2,4\text{-}Cl_2C_6H_3O_2CNHCH_2O$	73
$o\text{-}C_6H_4(CO)_2NCH_2OC_4H_9\text{-}n$	71 (78)		
$o\text{-}C_6H_4(CO)_2NCH_2OC_4H_9\text{-}i$	71 (48)	$1\text{-}C_{10}H_7O_2CNHCH_2O$	73

Carbonyl Compounds (contd.)

	2C₆H₅O₂CNCH(CH₃)₂O	p-ClC₆H₄NHCONClCH₂O (p-ClC₆H₄NHCONHCH₂)₂O		
			73	
			55 (83)	
			53	
		CH₂NCH₂OCH₃	447 (66), 450 (56)	
		CO		
		CH₂NCH₂OC₂H₅		
		CO		
		CH₂NCH₂OC₂H₅	447 (40)	
		CO		
		CH₂NCH₂OC₃H₇-n		
			450	
		CH₂NCH₂OCH₃		
		CO	219 (69), 484	
		CH₂NCH₃		
		CH₂NCH₂OCH₃		
		CO	219 (92)	
		CH₂NC₂H₅		

Carbonyl Compound		73
2C₆H₅O₂CNCH₂OCH₃		
H₂NCONHC₂H₅		62, 219 (99), 62
H₂NCONHC₂H₅		219 (55)
CONHCH₂OCH₃		62, 149,
		219, 446, 482 (86), 463
CO[N(CH₃)OCH₃]₂		
CO[N(CH₃)OCH₃-n]₂		219 (81), 446
CO[N(CH₃)OC₂H₅]₂		219 (85), 446
CO[N(CH₃)OC₃H₇-n]₂		482
CO[N(CH₃)OC₂H₅-i]₂		219 (50), 446
CO[N(CH₃)OC₃H₇-n]₂		482 (60)
CO[N(CH₃)OC₄H₉-n]₂		219 (45), 446
CO[N(CH₃)OC₄H₉-i]₂		446
CO[N(CH₃)OC₄H₉-i]₂		446
CO[N(CH₃)OC₄H₉-n]₂		446
CO[N(CH₃)OC₄H₉-n]₂		446
CO[N(CH₃)OC₅H₁₁-n]₂		219 (40)
[H₂NCONH(CH₃)CH₂]₂		146, 147, 149
CH₂[NCONH(OCH₃)]₂		62, 219 (63),
		453
		54, 453
(C₂H₅NCONHCH₂)₂O		54, 453
CH₃NCONHCH₂]₂O		357, 484
(CH₃)₃NCONHCH₂OCH₃		219 (53)
C₂H₅NHCONHCH₂OCH₃		55 (83)
C₂H₅NHCONHC₂H₄OCH₃-i		55 (86)
C₃H₇NHCONHCH₂OCH₃		55 (84)
(C₂H₅NHCONHCH₂)₂O		55 (86)
(C₃H₇NHCONHCH₂)₂O		54, 55
p-C₂H₅NHCONHC₆H₄OCH(CH₃)OC₂H₅-n		73

Note: References 385 to 537 are on pp. 266–269.

TABLE XXIV—Continued

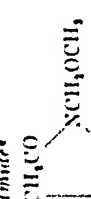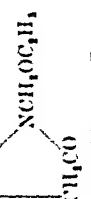### ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
Carbamyl Compounds (contd.)			
CH₃NCH₂OCH₃	92, 219 (99), 357, 484	(benzene ring, CO, NCH₂OCH₃ / NCH₂OCH₃)	180 (41)
CH₃NCH₂OCH₃ / CH₂NCH₂OCH₃	485 (64)	(benzene ring, CO, NCH₂OCH₃ / NCH₂OC₂H₅)	180 (82)
CH₃NCH₂OCH₃ / CH₂NCH₂OCH₃ (CH₃)	485 (30)	(benzene ring, CS, NCH₂OCH₃ / NCH₂OCH₃)	240, 457
i-C₃H₇N (CO, CH₂NCH₂OCH₃)	485	(benzene ring, CS, NCH₂OC₂H₅ / NCH₂OC₂H₅)	179 (87)
HO(CH₂)₂N (CO, CH₂NCH₂OCH₃)	185 (92)	(benzene ring, CS, NCH₂OCH₂C₆H₅ / NCH₂OCH₂C₆H₅)	240
[COSCH₃ / CO / CH₂NH]₂ O			

Note: References 382 to 537 are on pp. 206–209.

TABLE XXV

Ethers of N-α-Alkylol Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides
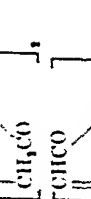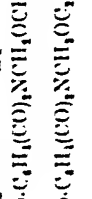
N-α-Alkylol Ether	References (Yield, %)	N-α-Alkylol Ether	References (Yield, %)
Aliphatic Amides			
HCONHCH(OCH₃)CCl₃	95	CH₃CICONH(OC₂H₄)OC₂H₄	231
		CH₃BrCONH(OC₂H₄)OC₂H₄	231
(HCONHCHCCl₂)₂O	95, 229	CH₃CONHC(OC₂H₄)OC₂H₄	231
		C₂H₅CONHCH(OCH₃)CBr₃	166
HCONHCHCH₂)₂O	207	(C₂H₅CONHCHCBr₂)₂O	166
CH₃CONHCH(OCH₃)CCl₃	95	C₂H₅CONHCH(OCH₃)CBr₃	207
		(C₂H₅CONHCHCBr₂)₂O	207
(CH₃CONHCHCCl₂)₂O	95, 229	C₂H₅CONHCH(OC₂H₄)OC₂H₄	207
		CH₃CONHC(OC₂H₄)=)C(C₂H₄)₁	231
(CH₃CONHCHCH₂)₂O	207	CH₂ClCH₂CONHCH(OC₂H₄)₁OₗС₁₀	231
		n-C₃H₇CONHCH(OCH₃)CCl₃	166
CH₃CONHCH(OCH₃)	223	(n-C₃H₇CONHCHCBr₂)₂O	166
CH₃CONHCH₂CH=)	231 (>70)	n-C₃H₇CONHCH(OОC₂H₄)CBr₃	207
CH₃CONHCH(OCH₃)	231 (>70)		
CH₃CONHC(OCH₃)=)C₆H₅	231 (>70)	n-C₄H₉CONHCH(OCH₃)CBr₃	207
CH₃CONHCH(OC₂H₄)=)C(C₂H₄)₁	231 (>70)	n-C₄H₉CONHCH(OCH₃)CBr₃	207
CH₃CONHC(OC₂H₄)₁=)C(C₂H₄)₁₀	231 (>70)		
		(n-C₄H₉CONHCHCBr₂)₂O	207
CH₃CONHCH(OCH₃)		n-C₄H₉CONHCH(OCH₃)CBr₃	207
	231	n-C₄H₉CONHCH(OCH₃)CBr₃	207
NHCOCH₃			
		(n-C₄H₉CONHCHCBr₂)₂O	207
		n-C₄H₉CONHCH(OCH₃)CBr₃	207
CH₃CONH(C₂H₄)CH(OCH₂)C₂H₅	216 (62)	n-C₄H₉CONHCH(OCH₃)CBr₃	231
CH₃CONHCH(OCH₃)CH₃H₅	231		

Note Reference 392 to 537 are on pp. 265–269.

TABLE XXV—Continued

ETHERS OF N-α-ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

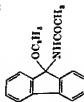| N-α-Alkylol Ether	References (Yield, %)	N-α-Alkylol Ether	References (Yield, %)
Aliphatic Amides (contd.)		$2:CH_3O\cdot5\cdot ClC_6H_3CONHCH(OC_2H_5)CCl_3$	206
c		$2:CH_3O\cdot5\cdot ClC_6H_3CONHCH(OC_4H_9)CCl_3$	208
$n\text{-}C_3H_7CONHCH\cdot CHBr_2)_2O$	207		
$(C_3H_7CONHCH(OCH_3)CBr_3$	207	$(2:CH_3O\cdot5\cdot ClC_6H_3CONHCH(OCH_3)CCl_3$	228
$n\text{-}C_3H_7CONHCH(OCH_3)CCl_3$	106	$2:CH_3O\cdot3,5\cdot Cl_2C_6H_2CONHCH(OCH_3)CCl_3$	206, 226
$C_3H_7OCCONHCH(OC_4H_9)CCl_3$	103	$2:CH_3O\cdot3,5\cdot Cl_2C_6H_2CONHCH(OC_2H_5)CCl_3$	208
$CONHCH(OC_2H_5)CCl_3$			
		$(2:CH_3O\cdot3,5\cdot Cl_2C_6H_2CONHCH(CCl_3)_2O$	226
Aromatic Amides		$2:CH_3O\cdot5\cdot BrC_6H_3CONHCH(OCH_3)CCl_3$	228
$C_6H_5CONHCH(OCH_3)CHCl_2$	208	$2:CH_3O\cdot5\cdot BrC_6H_3CONHCH(OC_2H_5)CCl_3$	205
		$2:CH_3O\cdot5\cdot BrC_6H_3CONHCH(OC_2H_5)CCl_3$	205
$C_6H_5CONHCH(CCl_3)_2O$	208		
$C_6H_5CONHCH(OCH_3)C\cdot HBr_2$	208	$(2:CH_3O\cdot5\cdot BrC_6H_2CONHCH(CCl_3)_2O$	228
		$2:CH_3O\cdot3,5\cdot Br_2C_6H_2CONHCH(OCH_3)CCl_3$	228
$(C_6H_5CONHCH(CHBr_2)_2O$	208		
$C_6H_5CONHCH(OCH_3)CCl_3$	95	$(2:CH_3O\cdot3,5\cdot Br_2C_6H_2CONHCH(CCl_3)_2O$	228
$C_6H_5CONHCH(OC_2H_5)CCl_3$	95	$2:CH_3O\cdot3\cdot O_2NC_6H_3CONHCH(OCH_3)CCl_3$	205, 225
$C_6H_5CONHCH(CHCl_3)_2O$	95, 229	$(2:CH_3O\cdot3\cdot O_2NC_6H_3CONHCH(CCl_3)_2O$	225
$C_6H_5CONHCH(OCH_3)CBr_3$	106	$2:CH_3O\cdot5\cdot O_2NC_6H_3CONHCH(OCH_3)CCl_3$	205, 225
		$2:CH_3O\cdot5\cdot O_2NC_6H_3CONHCH(OC_2H_5)CCl_3$	205
$(C_6H_5CONHCH(CHBr_2)_2O$	106		
$C_6H_5CONHCH(OC_2H_5)(C_3H_7)$	231	$(2:CH_3O\cdot5\cdot O_2NC_6H_3CONHCH(CCl_3)_2O$	225
$C_6H_5CONHCH(OC_4H_9)(C_3H_7)$	231	$o\text{-}CH_3C_6H_4CONHCH(OCH_3)CCl_3$	106, 108
$2:HO\cdot3,5\cdot Br_2C_6H_2CONHCH(OCH_3)CCl_3$	228	$o\text{-}CH_3C_6H_4CONHCH(OC_2H_5)CCl_3$	106
$2:HO\cdot3\cdot O_2NC_6H_3CONHCH(OCH_3)CCl_3$	225	$o\text{-}CH_3C_6H_4CONHCH(OC_4H_9)CCl_3$	106
$2:HO\cdot5\cdot Br\cdot3\cdot O_2NC_6H_2CONHCH(OCH_3)CCl_3$	225		
$2:HO\cdot3,5\cdot(O_2N)_2C_6H_2CONHCH(OCH_3)CCl_3$	106	$(o\text{-}CH_3C_6H_4CONHCH(CCl_3)_2O$	108
		$m\text{-}CH_3C_6H_4CONHCH(OCH_3)CCl_3$	106
$(2:CH_3O C_6H_4CONHCH(CHBr_2)_2O$	106	$m\text{-}CH_3C_6H_4CONHCH(OC_2H_5)CCl_3$	106
$2:CH_3O\cdot3\cdot ClC_6H_3CONHCH(OCH_3)CCl_3$	228	$m\text{-}CH_3C_6H_4CONHCH(OC_2H_5)CCl_3$	106
$2:CH_3O\cdot5\cdot ClC_6H_3CONHCH(OCH_3)CCl_3$	206, 226	$m\text{-}CH_3C_6H_4CONHCH(OC_4H_9CH_2O)CCl_3$	106

Aromatic Amides (contd.)

Structure	Ref. (yield)
$(m\text{-}CH_3C_6H_4CONHCH_2)_2O$	163
$p\text{-}CH_3C_6H_4CONHCH(OC_2H_5)CCl_3$	106
$p\text{-}CH_3C_6H_4CONHCH(OC_2H_5)CCl_3$	106
$p\text{-}CH_3C_6H_4CONHCH(OC_6H_5)CCl_3$	106

$\begin{array}{c} CH_3CO \\ \diagdown \\ \diagup \\ CH_3CO \end{array} NCH(OC_6H_5,n)CH_3$ — 232 (95)

$(p\text{-}CH_3C_6H_4CONHCH_2)_2O$ — 168

$\begin{array}{c} CH_3CO \\ \diagdown \\ \diagup \\ CH_3CO \end{array} NCH(OC_6H_4,i)CH_3$ — 232 (79)

Structure	Ref. (yield)
[furan]$CONHCH(OC_2H_5)CCl_3$	204 (80)
[furan]$CONHCH(OC_6H_5)CCl_3$	204 (70)

$\begin{array}{c} CH_3 \\ \diagdown \\ \end{array}\ NCH(OC_6H_5,n)CH_3$
$NCH(OC_6H_5,i)CH_3$
$NCH(OC_2H_5)CH_2Br$ — 232 (91)

Structure	Ref. (yield)
O_2N[furan]$CONHCH(OC_2H_5)CCl_3$	204 (92)
O_2N[furan]$CONHCH(OC_6H_5)CCl_3$	204 (57)

Carbamyl Compounds

Structure	Ref. (yield)
$o\text{-}C_2H_5O(CO)_2NCH(OC_6H_5)CH_3$	232 (82)
$o\text{-}CH_3O(CO)_2NCH(OC_6H_5,i)CH_3$	232 (41)
$o\text{-}CH_3O(CO)_2NCH(OC_2H_5)CH_2Br$	214 (63)

Carbamyl Compounds

Structure	Ref. (yield)
$CH_3O\cdot CNHCH(OC_2H_5)CCl_3$	73, 95
$CH_3O\cdot CNHCH(OC_2H_5)CCl_3$	204 (100)
$(CH_3O\cdot CNHCHCCl_3)_2O$	95
$CH_3O\cdot CNHCH(OC_6H_5,n)CH_3$	234 (79)
$CH_3O\cdot CNHCH(OC_6H_5,i)CH_3$	94
$CH_3O\cdot CNHCH(OC_2H_5)CCl_3$	94

Lactams and Imides

$\begin{array}{c} CH_3CO \\ \diagdown \\ \diagup \\ CH_2CH_3 \end{array} NCH(OC_2H_5)CCl_3$ — 101 (50)

Structure	Ref. (yield)
$(C_2H_5O_2CNHCH_2)_2O$	94, 95, 229, 230
$C_2H_5O_2CNHCH(OCH_3)CH_2\cdot CH=CH_2\cdot CH(NHCO_2C_2H_5)_2$	223
$C_2H_5O_2CNHCH(OCH_3)CH_2\cdot CH(NHCO_2C_2H_5)_2$	223

$\begin{array}{c} CH_3CO \\ \diagdown \\ \diagup \\ CH_3 \end{array} NCH(OC_2H_5)CH_3$ — 232 (93)

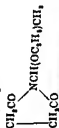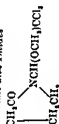| Structure	Ref. (yield)
$(C_2H_5O_2CNHCH_2)_2CH_2$	223
$n\text{-}C_4H_9O_2CNHCH(OC_2H_5)CH(NHCO_2C_4H_9,n)_2$	216 (62)
	223 (good)

TABLE XXV—*Continued*

ETHERS OF N-α-ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N-α-Alkylol Ether	References (Yield, %)	N-α-Alkylol Ether	References (Yield, %)
Carbamyl Compounds (contd.)		$C_2H_5NHCONHCH(OC_3H_7-n)CCl_3$	163
		$C_2H_5NHCONHCH(OC_4H_9-n)CCl_3$	163
$(i-C_4H_9O_2CNHCHCCl_3)_2O$	95		
$1-c_{10}H_7O_2CNHCH(OCH_3)CCl_3$	73	$(C_2H_5NHCONHCHCCl_3)_2O$	163
$2-c_{10}H_7O_2CNHCH(OCH_3)CCl_3$	73	$C_6H_5NHCONHCH(OC_4H_9-n)CH_3$	234
$H_2NCONHCH(OCH_3)CCl_3$	161	$C_2H_5NHCONHCH(OCH_3)CCl_3$	161
$H_2NCONHCH(OC_2H_5)CCl_3$	161	$C_6H_5NHCONHCH(OC_2H_5)CCl_3$	161
$H_2NCONHCH(OC_3H_7-n)CCl_3$	161		
$H_2NCONHCH(OC_4H_9-n)CCl_3$	161	$(C_6H_5NHCONHCHCCl_3)_2O$	161
		$C_6H_5NHCONHCH(OCH_3)CBr_3$	163
		$C_6H_5NHCONHCH(OC_2H_5)CBr_3$	163
$(H_2NCONHCHCCl_3)_2O$	161, 473		
$H_2NCONHCH(OCH_3)CBr_3$	162	$(C_6H_5NHCONHCHCBr_3)_2O$	163
$H_2NCONHCH(OC_2H_5)CBr_3$	162	$p-ClC_6H_4NHCONHCH(OC_4H_9-n)CH_3$	234 (90)
$H_2NCONHCH(OC_3H_7-n)CBr_3$	162	$m-O_2NC_6H_4NHCONHCH(OCH_3)CCl_3$	227
		$m-O_2NC_6H_4NHCONHCH(OC_2H_5)CCl_3$	227
$(H_2NCONHCHCBr_3)_2O$	162	$(m-O_2NC_6H_4NHCONHCHCCl_3)_2O$	227
		$p-O_2NC_6H_4NHCONHCH(OCH_3)CCl_3$	227
		$p-O_2NC_6H_4NHCONHCH(OC_2H_5)CCl_3$	227
$(CSNHCONCHCCl_3)_2O$	161		
$CH_3NHCONHCH(OC_2H_5)CCl_3$	163	$(p-O_2NC_6H_4NHCONHCHCCl_3)_2O$	227
		$o-CH_3C_6H_4NHCONHCH(OCH_3)CCl_3$	227
$(CH_3NHCONHCHCCl_3)_2O$	163	$o-CH_3C_6H_4NHCONHCH(OC_2H_5)CCl_3$	227
$CH_3NHCONHCH(OC_2H_5)CBr_3$	163		
		$(o-CH_3C_6H_4NHCONHCHCCl_3)_2O$	227
$(CH_3NHCONHCHCBr_3)_2O$	163	$p-CH_3C_6H_4NHCONHCH(OCH_3)CCl_3$	227
$C_2H_5NHCONHCH(OCH_3)CCl_3$	163	$p-CH_3C_6H_4NHCONHCH(OC_2H_5)CCl_3$	227
$C_2H_5NHCONHCH(OC_2H_5)CCl_3$	163		

Carbonyl Compounds (contd.)

(p-CH₃C₆H₄NHCONHCHCO)₂O	227	CCl₃CH(OCOC₄H₉NHCONHCCl₃	100
CH₃CONHCONH(OCH₃)₃CCl₃	101	CCl₃CHOINHCONHCONHCCl₃	
CH₃CONHCONH(OC₄H₉)CCl₃	101		
CH₃CONHCONH(OCH₃)₃CCl₃	161	CH₃NCH(OCH₃)₃CH₃	224
CO·NH(CH(OCH₃)₃CCl₃	161	CO	
CO·NH(CH(OC₃H₇-n)CCl₃	160, 161	CH₃NH	
CO·NH(CH(OC₄H₉-n)CCl₃	161		
CO·NH(CH(OC₄H₉)₃CCl₃	102	CH₃NCH(OC₄H₇-n)CH₃	224
CO·NH(CH(OC₄H₉)₃CMe₃	102	CO	
		CH₃NH	
NH·CH(OCH₃)₃CCl₃	102	CH₃NCH(OCH₃)₃CH₃	224
CO		CO	
NHCH(OC₃H₇)₃CCl₃		CH₃NCH(OC₄H₉-n)CH₃	224
CO		CO	
NHCH(OC₄H₉)₃CCl₃	102	CH₃NCH(OC₄H₉-n)CH₃	224
CO			
NHCH(OC₄H₉)₃CH₃	102	*Sulfonamides*	
[CCl₃CHCOCOCH₃)₂NHCONH(CHCCl₃)]₂O	100	p-CH₃C₆H₄SO₂N(CH₂CH(OC₄H₉-n)CH₃	232 (84)

Note. References 382 to 537 are on pp. 206-208.

TABLE XXVI

Esters of N-Methylol Derivatives of Amides, Lactams, Imides, and Carbamyl Compounds

N-Methylol Ester	References (Yield, %)	N-Methylol Ester	References (Yield, %)
Amides and Lactams			
$CH_3CON(CH_3)CH_2OCOCH_3$	244 (21)		
$C_2H_5CON(CH_3)CH_2OCOCH_3$	70 (90)		
$C_2H_5(C^2H_3)CONHCH_2OCOCH_3$	70		
$n\text{-}C_3H_7CONHCH_2OCOCH_3$	222		
$n\text{-}C_3H_7CONHCH_2OCOCH_3$	138 (99), 226		
$CH_2 \cdot C(CH_3)CONHCH_2OCOCH_3$	235		
$CH_2 \cdot C(CH_3)CONHCH_2OCOC_2H_5$	477 (91)		
	477		
	242		
$C_6H_5CON(CH_2OCOC_2H_5)_2$			
$C_6H_5CO_2C_6H_4 \cdot N$ (piperazine-dione) $NCH_2OCOC_2H_5$	95 (50)	CHCO $\diagup$ $=$ $\diagdown$ CHCO	NCH₂OCOCH=CHCH₃ 8 (34)
Imides		CHCO $\diagup$ $=$ $\diagdown$ CHCO	NCH₂OCOC₆H₅ 8 (90)
CH₃CO (cyclopropane) NCH₂OCOCH₃	98 (75)	CHCO $\diagup$ $=$ $\diagdown$ CHCO	NCH₂OCONHC₆H₅ 8 (21)
CH₃CO (cyclopropane) NCH₂OCOCH₃	8 (93)	$o\text{-}C_6H_4(CO)_2NCH_2OCOH$	220 (24)
		$o\text{-}C_6H_4(CO)_2NCH_2OCOC_6H_5$	243
		Carbamyl Compounds	
CHCO (cyclopropane) NCH₂OCOCH₃		(cyclohexane fused) O–CS NCH₂OCOCH₃ (DL-*trans*)	181 (65)
		(cyclohexane fused) O–CS NCH₂OCOC₆H₅ (DL-*trans*)	181 (55)
		(cyclohexane fused) O–CS NCH₂OCONHC₆H₅ (DL-*trans*)	181 (65)

Carbonyl Compounds (contd.)			
	194 (75)		237
	178 (56)		238
	178 (50)		240
	239		240, 457
	239		238
	238		240
	238		237
	237		241

TABLE XXVII

Esters of N-α-Alkylol Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

| N-α-Alkylol Ester	References (Yield, %)	N-α-Alkylol Ester	References (Yield, %)
Aliphatic Amides		[CONHCH(OCOCH₃)CCl₃]₂	163
HCONHCH(OCOCH₃)CBr₃	207	C₂H₅CH(CONHC₆H₅)CONHCH(OCOCH₃)CCl₃	163
HCONHCH(OCOC₂H₅)CBr₃	207	C₂H₅CH(CONHCH(OCOCH₃)CCl₃)₂	163
CH₃CONHCH(OCOC₂H₅)CCl₃	106	CCl₃CH(OCOCH₃)CH(CONHC₆H₅)CONHCH-	
CH₃CONHCH(OCOCH₃)CBr₃	106	(OCOCH₃)CCl₃	163
CH₃CONHCH(OCOC₂H₅)CBr₃	207		
C₂H₅CH₂CONHCH(OCOCH₃)CCl₃	106	*Aromatic Amides*	
C₂H₅CH₂CONHCH(OCOC₂H₅)CCl₃	106	C₆H₅CONHCH(OCOCH₃)CHCl₂	208
C₂H₅CH₂CONHCH(OCOCH₃)CBr₃	106	C₆H₅CONHCH(OCOC₂H₅)CHCl₂	208
C₂H₅CH₂CONHCH(OCOC₂H₅)CBr₃	106	C₆H₅CONHCH(OCOCH₃)CHBr₂	208
NCCH₂CONHCH(OCOCH₃)CCl₃	103	C₆H₅CONHCH(OCOCH₃)CCl₃	95, 106
C₂H₅CONHCH(OCOCH₃)CBr₃	207	C₆H₅CONHCH(OCOC₂H₅)CCl₃	95
C₂H₅CONHCH(OCOC₂H₅)CBr₃	207	C₆H₅CONHCH(OCOCH₃)CBr₃	106
n-C₃H₇CONHCH(OCOCH₃)CCl₃	106	C₆H₅CONHCH(OCOC₂H₅)CBr₃	106
n-C₃H₇CONHCH(OCOC₂H₅)CCl₃	106	2-CH₃CO₂C₆H₄CONHCH(OCOCH₃)CCl₃	100
n-C₃H₇CONHCH(OCOCH₃)CBr₃	207	2-CH₃CO₂-3-ClC₆H₃CONHCH(OCOCH₃)CCl₃	220
n-C₃H₇CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃CO₂-5-ClC₆H₃CONHCH(OCOCH₃)CCl₃	226
i-C₃H₇CONHCH(OCOCH₃)CBr₃	207	2-CH₃CO₂-3,5-Cl₂C₆H₂CONHCH(OCOCH₃)CCl₃	220
i-C₃H₇CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃CO₂-3-BrC₆H₃CONHCH(OCOCH₃)CCl₃	220
i-C₃H₇CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃CO₂-5-BrC₆H₃CONHCH(OCOCH₃)CCl₃	228
n-C₄H₉CONHCH(OCOCH₃)CBr₃	207	2-CH₃CO₂-3,5-Br₂C₆H₂CONHCH(OCOCH₃)CCl₃	228
n-C₄H₉CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃CO₂-3-O₂NC₆H₃CONHCH(OCOCH₃)CCl₃	228
n-C₄H₉CONHCH(OCOCH₃)CBr₃	207	2-CH₃CO₂-3-O₂N-5-BrC₆H₂CONHCH(OCOCH₃)CCl₃	228
n-C₄H₉CONHCH(OCOC₂H₅)CBr₃	207	2-C₆H₅CO₂-3,5-Cl₂C₆H₂CONHCH(OCOC₆H₅)CCl₃	225
n-C₄H₉CONHCH(OCOCH₃)CBr₃	207	2-C₆H₅CO₂-5-BrC₆H₃CONHCH(OCOC₆H₅)CCl₃	225
n-C₄H₉CONHCH(OCOC₂H₅)CBr₃	207	2-C₆H₅CO₂-3,5-Br₂C₆H₂CONHCH(OCOC₆H₅)CCl₃	226
n-C₄H₉CONHCH(OCOCH₃)CBr₃	207	2-CH₃OC₆H₄CONHCH(OCOCH₃)CBr₃	225
n-C₄H₉CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃OC₆H₄CONHCH(OCOCH₃)CBr₃	100
n-C₄H₉CONHCH(OCOC₂H₅)CBr₃	207	2-CH₃O-3-ClC₆H₃CONHCH(OCOCH₃)CCl₃	220
CCl₃CHOHCONHCH(OCOC₂H₅)CCl₃	172	2-CH₃O-5-ClC₆H₃CONHCH(OCOCH₃)CCl₃	220
		2-CH₃O-5-ClC₆H₃CONHCH(OCOC₆H₅)CCl₃	200
Amides of Dicarboxylic Acids		2-CH₃O-3,5-Cl₂C₆H₂CONHCH(OCOCH₃)CCl₃	226
C₂H₅O₂CCONHCH(OCOCH₃)CCl₃	100	2-CH₃O-5-BrC₆H₃CONHCH(OCOCH₃)CCl₃	228
C₂H₅NHCOCONHCH(OCOC₂H₅)CCl₃	163	2-CH₃O-3,5-Br₂C₆H₂CONHCH(OCOCH₃)CCl₃	228
		2-CH₃O-3,5-Br₂C₆H₂CONHCH(OCOC₆H₅)CCl₃	228

Aromatic Amides (contd.)

Compound	Ref.
2 CH₃O,3-NC₆H₃CONHCH(OCOCH₃)₂CCl₃	225
2 CH₃O,5-O₂NC₆H₃CONHCH(OCOCH₃)₂CCl₃	225
2 CH₃O,4,6-... CONHCH(OCOCH₃)₂CCl₃	225
2 CH₃,4,6-... CONHCH(OCOCH₃)₂CCl₃	225
o CH₃C₆H₄CONHCH(OCOCH₃)₂CCl₃	158
o CH₃C₆H₄CONHCH(OCOCH₃)₂CCl₃	158
m CH₃C₆H₄CONHCH(OCOCH₃)₂CCl₃	158
p CH₃C₆H₄CONHCH(OCOCH₃)₂CCl₃	158

Compound	Ref.
C₆H₅COSNHCH(COOC₆H₄)₂CCl₃	204 (60)
Br...COSNHCH(COOC₆H₄)₂CCl₃	204 (43)

Lactams and Imides

Compound	Ref.
CH₂·CH₂·CCH(OCOCH₃)₂CCl₃	101 (90)
CH₂·CH₂·CCH(OCOCH₃)₂CCl₃	101 (56)
o-C₆H₄(CO)₂NCH(OCOCH₃)₂CH₂CH₃	211 (95)

Carbamyl Compounds

Compound	Ref.
C₆H₅CH₂CNHCH(OCOCH₃)₂CCl₃	94 (80)
CO₂CH=NCSNHCH(OCOCH₃)₂CCl₃	100
CO·NHCH(OCOCH₃)₂CCl₃	161
CO·NHCH(OCOCH₃)₂CCl₃	162
CO·NHCH(OCOCH₃)₂CBr₃	161
CH₂·CONHCH(OCOCH₃)₂CCl₃	162
CH₂·CONHCH(OCOCH₃)₂CBr₃	162
CH₂·CON(CH₃)CH(OCOCH₃)₂CCl₃	163
CH₂·CON(C₂H₅)CH(OCOCH₃)₂CCl₃	163
CH₂·CON(C₃H₇)CH(OCOCH₃)₂CCl₃	163
CH₂·CON(C₂H₄OH)CH(OCOCH₃)₂CCl₃	163
CH₂·CON(C₆H₅)CH(OCOCH₃)₂CCl₃	163
CH₂·CON(C₆H₅NO₂-m)CONHCH(OCOCH₃)₂CCl₃	227
CH₂·CON(C₆H₅·p)CONHCH(OCOCH₃)₂CCl₃	227
CH₂·CON(C₆H₅)CONHCH(OCOCH₃)₂CCl₃	227
CH₂·CON(C₆H₄·p)CONHCH(OCOCH₃)₂CCl₃	227

Sulfonamides

Compound	Ref.
C₆H₅CH₂SO₂NHCH(OCOCH₃)₂CCl₃	159
C₆H₅SO₂NHCH(OCOCH₃)₂CCl₃	159
p-CH₃C₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
p-CH₃C₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
p-ClC₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
p-CH₃C₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
m-CH₃C₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
p-O₂NC₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
p-C₆H₄C₆H₄SO₂NHCH(OCOCH₃)₂CCl₃	159
2,4,6-(CH₃)₃C₆H₂SO₂NHCH(OCOCH₃)₂CCl₃	159

Compound	Ref.
SO₂NHCH(OCOCH₃)₂CCl₃	169

TABLE XXVIII

N-Halomethyl, and N-α-Haloalkyl, Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

$$RCON(R')CH(R'')OH \rightarrow RCON(R')CH(R'')X$$

N-α-Haloalkyl Derivatives	Method*	References (Yield, %)
Amides		
HCONHCH₂Cl	PCl₅, dioxane	96
HCONHCHClCCl₃	PCl₅, (C₂H₅)₂O	101 (76)
	PCl₅, heat	160
HCONHCHClCBr₃	PCl₅, heat	207
CH₃CONHCH₂Cl	PCl₅, dioxane	96
	CH₃CONH₂, (CH₂O)ₓ, HCl, CH₃CO₂H	202 (60), 203 (60)
	CH₃CONH₂, (CH₂O)ₓ, HCl, dioxane	201
	PBr₅, dioxane	96
CH₃CONHCH₂Br	CH₃CONH₂, CH₃CHO, HCl, dioxane	201
CH₃CONHCHClCH₃	PCl₅, heat	209
CH₃CONHCHClCCl₃	CH₃CONHCH=CCl₂, Cl₂, CHCl₃	209
	PCl₅, heat	207
CH₃CONHCHClCBr₃	CH₃CONH₂, n-C₃H₇CHO, HCl, dioxane	201
CH₃CONHCH(CH₂)₂CH₃	PCl₅, dioxane, 30–40°	32
CH₃CON(CH₃)CH₂Cl	PCl₅, dioxane, 30–40°	32
CH₃CON(C₃H₇-n)CH₂Cl	PCl₅, dioxane, 30–40°	32 (good)
CH₃CON(C₃H₇-i)CH₂Cl	PCl₅, dioxane, 30–40°	32
CH₃CON(CH₂C₆H₅)CH₂Cl	CH₃CONHR, (CH₂O)ₓ, HCl, C₆H₆	196
CH₃CON(C₁₁H₂₃-n)CH₂Cl	CH₃COCl, CH₃N=CHC₆H₅	216
CH₃CON(CH₃)CHClC₆H₅	PCl₅, (C₂H₅)₂O/dioxane	96
CH₂ClCONHCH₂Cl	PCl₅, heat	207
CH₂ClCONHCH₂Cl	PCl₅, (C₂H₅)₂O	100, 186 (76)
CCl₃CONHCH₂Cl	PCl₅, dioxane	96
C₃H₇CONHCH₂Cl		

$C_6H_5CONHCH_2Br$	PBr_3, dioxane	96
$C_6H_5CONHCHClCH_3$	PCl_5, heat	207
$n\text{-}C_3H_7CONHCHClCH_3$	PCl_5, heat	207
$n\text{-}C_7H_{15}CONHCH_2Cl$	$RCONH_2$, $(CH_2O)_n$, HCl, CH_3Cl	196
	$RCONH_2$, $(CH_2O)_n$, HCl, C_2H_5	195
$n\text{-}C_7H_{15}CON(CH_2)CH_2Cl$	$RCONH_2$, $(CH_2O)_n$, HCl, C_2H_4	200
$n\text{-}C_9H_{19}CON(CH_2)CH_2Br$	$RCONHCH_2$, $(CH_2O)_n$, HCl, C_2H_5	190
$n\text{-}C_{11}H_{23}CONHCH_2Cl$	$RCONHCH_2$, $(CH_2O)_n$, HBr, C_4H_9	196
	$(RCONH)_2CH_2$, $(CH_2O)_n$, HCl, C_2H_4	198, 199
$n\text{-}C_{17}H_{35}\cdot CONH\cdot CH_2Cl$	$RCONH_2$, $(C_2H_5O)_2$	197
$C_6H_5CONHCH_2Cl$	C_6H_5CONH, $(CH_2O)_n$, HCl, CH_3CO_2H	96 (78), 100
$C_6H_5CONHCH_2Cl$	PBr_3, $(C_2H_5)_2O$	202 (62)
	$C_6H_5CONHCH=CCl_2$, HCl	96 (80)
$C_6H_5\cdot CH_2\cdot CONH\cdot CH_2Cl$	$C_6H_5CONHCH=CCl_2$, HBr	208
$C_6H_5CONHCHClCH_2Cl$	PCl_5, $(C_2H_5)_2O$/dioxane	208
$C_6H_5CONHCHClCH_3$	PCl_5, $(C_2H_5)_2O$/dioxane	101 (72)
$C_6H_5CONHCHClCCl_3$	PCl_5, dioxane, 30–40°	32
$C_6H_5CON(CH_3)CHClCH_3$	C_6H_5COCl, $CH_3N=CHCH_3$	216 (55)
$2,4\text{-}Cl_2C_6H_3CONHCH_2Cl$	PCl_5, dioxane	96
$2\text{-}CH_3\text{-}5\text{-}ClC_6H_3CONHCHClCCl_3$	PCl_5, heat	206 (94)
$2\text{-}CH_3\text{-}3,5\text{-}Cl_2C_6H_2CONHCHClCCl_3$	PCl_5, heat	206
$2\text{-}CH_3O\text{-}5\text{-}BrC_6H_3CONHCHBrCCl_3$	PCl_5, heat	205
$2\text{-}CH_3O\text{-}5\text{-}BrC_6H_3CONHCH_2Cl$	PBr_3, heat	205
$2\text{-}CH_3O\text{-}3,5\text{-}Br_2C_6H_2CONHCHClCCl_3$	PCl_5, heat	205
$2\text{-}CH_3O\text{-}5\text{-}O_2NC_6H_3CONHCHClCCl_3$	PCl_5, heat	205
$\cdot CH_2C_6H_5CONHCHClCCl_3$	PCl_5, heat	106

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXVIII—Continued

N-Halomethyl and N-α-Haloalkyl Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

$$RCON(R')CH(R'')OH \rightarrow RCON(R')CH(R'')X$$

N-α-Haloalkyl Derivatives	Method*	References (Yield, %)
Amides (contd.)		
$m\text{-}CH_3C_6H_4CONHCHClCICCl_3$	PCl_5, heat	106
$p\text{-}CH_3C_6H_4CONHCHClCICCl_3$	PCl_5, heat	106
$C_2H_5O_2CNHCHClCICCl_3$	PCl_5, heat	160
$C_2H_5O_2CNHCHBrCCl_3$	PBr_5, heat	100
$(CONHCHClCCl_3)_2$	PCl_5, heat	163
(ring)—$CONHCHClCICCl_3$	PCl_5, heat	204
O_2N—(ring)—$CONHCHClCICCl_3$	PCl_5, heat	204
Lactams		
CH_2CO / CH_2CH_2 ring—NCH_2Cl	$SOCl_2$	177 (85), 184 (87)
	PCl_5, $(C_2H_5)_2O$/dioxane	33
CH_2CO / CH_2CH_2 ring—$NCHClCCl_3$	PCl_5, $(C_2H_5)_2O$/dioxane	101 (99)

Structure	Reagent/Conditions	Reference (Yield)
CH_3CH_2CO ... NCH_2Cl ... $CH_3CH_2CH_2$	$SOCl_2$, C_6H_6	184 (70)
	PCl_5 ($C_2H_5)_2O$/dioxane	33
Imides		
CH_2CO NCH_2Cl (from $ClCH_2N$, two $=O$)	PCl_5, CH_3COCl, CCl_4	1, 65 (91)
CH_2CO NCH_2Cl CH_2CO	PCl_5, $CHCl_3$	66 (75)
CH_2CO NCH_2Br CH_2CO	PBr_3, C_6H_6	188 (91)
$ClHCCO$ NCH_2Cl CH_2CO	PBr_3, $CHCl_3$	66
	N-Chloromethylmaleimide, HCl	8

Note. References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXVIII—*Continued*

N-Halomethyl and N-α-Haloalkyl Derivatives of Amides, Lactams,
Imides, Carbamyl Compounds, and Sulfonamides

RCON(R')CH(R'')OH → RCON(R')CH(R'')X

N-α-Haloalkyl Derivatives	Method*	References (Yield, %)
Imides (contd.)		
CHCO ＼ NCH₂Cl ／ CHCO	PCl₃, (CH₃)₂CO	8 (81)
CHCO ＼ NCH₂Br ／ CHCO	PBr₃, (CH₃)₂CO	8 (52)
o-C₆H₄(CO)₂NCH₂Cl	PCl₅, (C₂H₅)₂O	97 (82)
	o-C₆H₄(CO)₂NH, (CH₂O)ₓ, HCl,	202 (70)
	CH₃CO₂H	192, 193
	Concd. HCl, heat	192
	o-C₆H₄(CO)₂NCH₂COCl, heat (−CO)	190 (90)
	o-C₆H₄(CO)₂NCH₂OC₂H₅, CH₃COCl	191 (81)
	o-C₆H₄(CO)₂NCH₂N⟨ring⟩, CH₃COCl	

o-C₆H₄(CO)₂NCH₂Br	PBr₃, C₆H₆	188 (82)
	o-C₆H₄(CO)₂NCH, Br₂, 170°	151 (100)
	Concd. HBr, heat	104 (69), 192, 193
	Concd. HBr, H₂SO₄, heat	70 (65)
	o-C₆H₄(CO)₂NCH₂N⟨ ⟩O, CH₂COBr	191 (86)
o-C₆H₄(CO)₂NCH₂I	Concd. HI, heat	192, 193
o-C₆H₄(CO)₂NCHClCH₃	o-C₆H₄(CO)₂NCH=CH₂, HCl, CHCl₃	211 (97)
o-C₆H₄(CO)₂NCHClCH₂Br	o-C₆H₄(CO)₂NCH(CH₃)CH₂Br, NBS†	214 (89)
o-C₆H₄(CO)₂NCHBrCHBrCH₃	o-C₆H₄(CO)₂NCH=CH₂, Br₂	210
o-C₆H₄(CO)₂NCH=CHCH₂Br	o-C₆H₄(CO)₂NCH=CHCH₃, Br₂	212
o-C₆H₄(CO)₂NC(CH₃)₂Br	o-C₆H₄(CO)₂NCH[CH₃]CH=CH₂, Br₂, P	212, 215 (62)
	o-C₆H₄(CO)₂NC(CH₃)₂=CH₂, Br₂	213
CO⟩N-CH₂Cl (ring)	PCl₃, (C₂H₅)₂O	99 (65)
	SOCl₂ (C₂H₅)₂O	182 (54)
Carbamyl Compounds		
ClOCNHCH₂Cl	OCONCl₂H, SOCl₂	73 (68)
HOCONHCHClCCl₃	OCNCHClCCl₃, SOCl₂	73
CH₃OCONHCHClCCl₃	OCNClCCl₃, CH₂OH	73
n-C₄H₉OCONHCHClCCl₃	HO.CNH₂, (CH₂O)ₓ, HCl, C₆H₅	197
CH₃O(C₃H₅C₆H₅-m)NCH₂Cl	CH₃OCNHH, (CH₂O)ₓ, HCl, C₄H₅	196
C₆H₅OCON(C₆H₅-n)CH₂Cl	CH₃OCNHH, (CH₂O)ₓ, HCl, C₆H₅	196
C₆H₅OCONC₆H₄(p-)CH(CH₃)CH₂Cl	C₆H₅O.CCl, ClCH₂=N–m	210
2,4-C₆H₃(CH₃)₂N(ClCH₂)CCl₃	OCNClCCl₃, 2,4-Cl₂C₄H₂OH	216
1-C₁₀H₇OCONHCHClCCl₃	OCNClCCl₃, 1-C₁₀H₇OH	73

Note. References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

† N-Bromosuccinimide.

TABLE XXVIII—Continued

N-Halomethyl and N-α-Haloalkyl Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

$$RCON(R')CH(R')OH \rightarrow RCON(R')CH(R')X$$

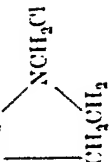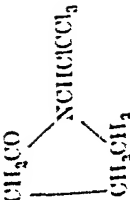| N-α-Haloalkyl Derivatives	Method*	References (Yield, %)
Carbamyl Compounds (contd.)		
$2\text{-}C_{10}H_7O_2CNHCHClCCl_3$ $O_2CNHCHClCCl_3$	$OCNCHClCCl_3$, $2\text{-}C_{10}H_7OH$	73
(quinolinyl structure)	$OCNCHClCCl_3$	73
$CS(NHCHClCCl_3)_2$	PCl_5, heat	100
CONCH₂Cl ring structure (CO / CH₂NH)	PCl_5, heat or concl. HCl	185 (65)
CO—NCH₂Cl ring structure ($C_6H_5C(CH_3)NH$)	PCl_5, $CHCl_3$	187 (60)
NCH₂Cl cyclohexane O-CS structure (DL-*trans*)	$SOCl_2$, $(C_2H_5)_2O$	181 (53)
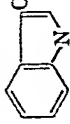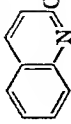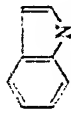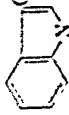
Structure	Reagent	Ref. (yield)
(benzene ring fused) NCH₂Cl, CO	Concd. HCl, heat	194 (91)
(benzene ring fused) NCH₂Cl, CS	SOCl₂	178 (60)
(benzene ring fused) NCH₂Cl, CS	SOCl₂, CHCl₃	183 (55)
(benzene ring fused) CO, NCH₂Cl	PCl₃, heat	189
(benzene ring fused) NCH₂Cl, CS	SOCl₂	180 (59)
(benzene ring fused) NCH₂Cl, CS	SOCl₂, heat	179 (55)

Sulfonamides

Structure	Reagent	Ref.
$C_6H_5SO_2NHCH_2Cl$	$C_6H_5SO_2NH_2$, $(CH_2O)_x$, HCl, dioxano	201
$C_6H_5SO_2N(CH_2Cl)CH_3$	$C_6H_5SO_2NH_2$, CH_3CHO, HCl, dioxane	201
$C_6H_5SO_2NHCH(Cl)CH(CH_3)_2CH_3$	$C_6H_5SO_2NH_2$, $n\text{-}C_3H_7CHO$, HCl, dioxano	201

Note   References 382 to 537 are on pp. 260–269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXIX

N-Aminomethyl Derivatives of Amides, Lactams, Imides, and Carbamyl Compounds*

$$RCONH_2 + CH_2O + R_2'NH \rightarrow RCONHCH_2NR_2'$$

N-Aminomethyl Derivative	References (Yield, %)	N-Aminomethyl Derivative	References (Yield, %)
$C_6H_5CH_2CONHCH_2N$⟨CH_2CH_2 CH_2CH_2⟩CH_2	388 (78)	(indolyl) $CH_2NHCOC_6F_5$	83
$CH_3\text{--}CHCONHCH_2N(CH_3)_2$	477	$CH_2NHCOC_6H_5$ $CONHCH_2N(C_2H_5)_2$	426
$C_6H_5CONHCH_2N$⟨CH_2CH_2 CH_2CH_2⟩CH_2	96 (72)	(quinolyl) $OC_4H_9\text{-}n$	
(indolyl) $CH_2NHCOC_6H_5$	83 (57)	$O=$ (piperidinedione with NCH_2N⟨CH_2CH_2 CH_2CH_2⟩CH_2) NCH_2N⟨CH_2CH_2 CH_2CH_2⟩CH_2	65 (85)
(benzimidazolyl) CH_3 $CH_2N(CH_3)_2$ $CH_2NHCOC_6H_5$	83 (74)	$NCHCO$ CH_2CO NCH_2N⟨CH_2CH_2 CH_2CH_2⟩CH_2 CH_3 CH_2CH_2	8 (49)
(indolyl) $CH_2NHCOC_6H_5$	83	From α-methylacrylamide and	
(indolyl) $CH_2N(CH_3)_3$ I⊖ $CH_2NHCOC_6H_5$	83	Dimethylamino	477
		Di-n-propylamino	477
		Di-n-butylamino	477
		Morpholino	477 (75)
		$CH_2NHCH_2CH_2OH$	477
		$HN(CH_2CH_2OH)_2$	477

From succinimide and		
Dimethylamine	46 (73)	Diethylamine	142 (42)
Piperidine	CA, 144	Di-n-propylamine	142 (42)
Morpholine	445 (50)	Di-n-butylamine	142 (42)
		Piperidine	142 (42)
		Morpholine	142 (41)

From maleimide and		
Diethylamine	432	$CH_2C_6H_5$
Di-n-butylamine	N (42), 432	
Piperidine	N (42), 432	
Aniline	N (42), 432	$CONCH_2N$ CO $CH_2C_6H_5$

467 (94)

From phthalimide and		
Dimethylamine	I (42), 412	
Piperidine	434	O
Aniline	431	CH_2NOCH_2 CO $CH_2C_6H_5$

467 (91)

From 3-(and 4-)Nitrophthalimide and	
Aniline	436
o-Chloroaniline	436
m-Chloroaniline	436
p-Chloroaniline	436
2,4-Dichloroaniline	436
o-Bromoaniline	436
m-Bromoaniline	436
p-Bromoaniline	436
o-Nitroaniline	436
m-Nitroaniline	436
p-Nitroaniline	436
4-Chloro-2-nitroaniline	436
5-Chloro-2-nitroaniline	436
2-Chloro-4-nitroaniline	436
p-Anisidine	436
o-Toluidine	436
m-Toluidine	436
p-Toluidine	436
2-Naphthylamine	436

$CONCH_2N$ CO NH C_6H_8

[Rt. (max) an]

From	
Diethylamine	260 (66)
Pyrroline	260 (66)
Morpholine	260 (66)
Aniline	260 (91)
p-Chloroaniline	260 (42)
p-Bromoaniline	260 (73)
m-Nitroaniline	260 (42)
o-Anisidine	260 (42)
p-Anisidine	260 (52)
o-Toluidine	260 (75)
p-Toluidine	260 (70)
m-Toluidine	260 (43)
p-Toluidine	260 (73)
2,3-Xylidine	260 (56)

From saccharin and	
Dimethylamine	182 (12)
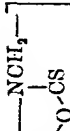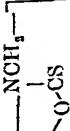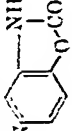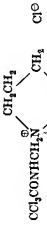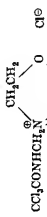
* For an exhaustive compilation of compounds of this class through 1958 see ref. 3

TABLE XXIX—Continued

N-Aminomethyl Derivatives of Amides, Lactams, Imides, and Carbamyl Compounds*

$$RCONH_2 + CH_2O + R_2'NH \rightarrow RCONHCH_2NR_2'$$

N-Aminomethyl Derivative	References (Yield, %)	N-Aminomethyl Derivative	References (Yield, %)
From [structure] and		From [structure] and	
Aniline	324 (84)	Piperidino	488 (85)
o-Chloroaniline	324 (73)	Morpholino	488 (77)
m-Chloroaniline	324 (82)		
p-Chloroaniline	324 (80)	From [NO₂ structure]	
2,1-Dichloroaniline	324 (38)	Morpholino	488 (81)
m-Bromoaniline	324 (88)		
p-Bromoaniline	324 (81)	From [structure] and	
3,1-Dibromoaniline	324 (60)	Diethylamino	183 (96), 489 (63)
o-Anisidine	324 (85)	Piperidino	183 (98), 189, 318
p-Anisidine	324 (87)	Morpholino	183 (86), 318
p-Phenetidine	324 (88)	Anilino	183 (88)
o-Phenylenediamine (bis cpd.)	324 (90)		
p-Phenylenediamine (bis cpd.)	324 (96)	[NCH₂—structure]₂ NC₅H₁₁	183 (54)
N-Acetyl-p-phenylenediamine	324 (84)		
o-Toluidine	324 (81)	NCH₂CH₂OH	183 (58)
m-Toluidine	324 (83)		
p-Toluidine	324 (87)		
3,1-Dimethylaniline	324 (58)		
2,4,5-Trimethylaniline	324 (70)		
2,4,6-Trimethylaniline	324 (59)		
2-Naphthylamine	324 (86)		
Benzidine (bis cpd.)	324 (97)		
2-Aminopyridine	324 (41)		
From [O₂N structure] and			
Piperidino	488 (80)		
Morpholino	488 (77)		
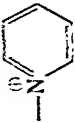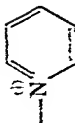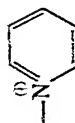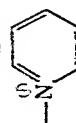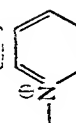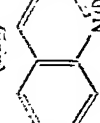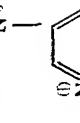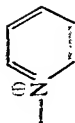
Note: References 382 to 637 are on pp. 266–269.
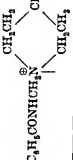
TABLE XXX

N-Quaternary Aminomethyl Derivatives of Amides, Imides, and Carbamyl Compounds

RCONHCH₂—N⊕ X⊖

RCONHCH₂—		References (Yield, %)
CH₃CONHCH₂—	⊕N⟨phenyl⟩ Cl⊖	140
CCl₃CONHCH₂—	CCl₃CONHCH₂N⟨piperidine⟩ Cl⊖	191 (83)
CCl₃CONHCH₂—	CCl₃CONHCH₂N⟨morpholine⟩ O Cl⊖	191 (87)
C₃H₅CONHCH₂—	⊕N⟨phenyl⟩ Cl⊖	140
n-C₁₁H₂₃CONHCH₂—	⊕N⟨phenyl⟩ Cl⊖	140

TABLE XXX—*Continued*

N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBAMYL COMPOUNDS

$$RCONHCH_2\text{—}\overset{\oplus}{N}\diagdown \quad X^{\ominus}$$

RCONHCH₂—		X⊖	References (Yield, %)
n-C₁₇H₃₅CONHCH₂—	(N-methylpyridinium)	Cl⊖	138 (78), 140, 200, 243
	(N-methylpyridinium)	NO₃⊖	140
	(N-methylpyridinium)	HSO₄⊖	140, 306
	(N-methylpyridinium)	HO₂CCO₂⊖	140
	(N-methylpyridinium)	p-CH₃C₆H₄SO₃⊖	140
	(N-phenylquinolinium)	Cl⊖	140
n-C₁₁H₂₃CONHCH₂—	(N-methylpyridinium)	Cl⊖	235

140

305

199

199

199

304 (92)

304 (84)

66

191 (94)

CH₃(CH₂)CH=CH(CH₂)₄CONCH CH₂—

n-C₁₄H₂₉CONCH₂ — CH₃

n-C₁₄H₂₉CONCH₂ — CH₃

n-C₁₄H₂₉CONCH₂ —

CH₂O NCH₄— CH₂O

C₆H₅CONCH₂—

TABLE XXX—*Continued*

N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBAMYL COMPOUNDS

$RCONHCH_2$—N⁺—X⁻   —N⁺—X⁻

$RCONHCH_2$—		References (Yield, %)
$C_6H_5CONHCH_2$— *(contd.)*		
	$C_6H_5CONHCH_2\overset{\oplus}{N}$ (ring: CH_2CH_2, CH_2, CH_2CH_2) $Br^\ominus$	191 (91)
	$C_6H_5CONHCH_2\overset{\oplus}{N}$ (ring: CH_2CH_2, CH_2, CH_2CH_2) $ClO_4^\ominus$	191 (49)
	$o\text{-}C_6H_4(CO)_2NCH_2\overset{\oplus}{N}$ (ring: CH_2CH_2, CH_2, CH_2CH_2) $Br^\ominus$	191 (83)
$o\text{-}C_6H_4(CO)_2NCH_2$—	—$\overset{\oplus}{N}(CH_3)_3$ $I^\ominus$	1, 304 (73)
	$\overset{\oplus}{N}$ (ring with CH_3, CH_2CH_2, CH_2, CH_2CH_2) $I^\ominus$	304 (96)

$C_2H_5OCONHCH_2$—

—NCH₂ (benzodioxole structure)

Structure	Reference (Yield)
CH_2CH_2 / $CH_3N^{\oplus}$—O / CH_2CH_2 I⁻	304 (87)
$C_5H_5N^{\oplus}$ Cl⁻	243 (good)
o-$C_6H_4(CO)_2NCH_2N(CH_3)_2$ Cl⁻	191 (73)
$C_5H_5N^{\oplus}$ Cl⁻	235
—$N^{\oplus}(CH_3)_3$ I⁻	194 (90)
—$N^{\oplus}(CH_3)_2C_2H_5$ I⁻	194 (72)
—$N^{\oplus}C_4H_7CH_3$ I⁻	194 (75)
CH_2 / CH_2CH_2 / $CH_3N^{\oplus}$ / CH_2CH_2 I⁻	194 (74)
CH_2CH_2 / $CH_3N^{\oplus}$—O / CH_2CH_2 I⁻	194 (80)

TABLE XXX—*Continued*

N-Quaternary Aminomethyl Derivatives of Amides, Imides, and Carbamyl Compounds

RCONHCH₂—	RCONHCH₂—$\overset{\oplus}{\text{N}}$— X⁻ $\overset{\oplus}{\text{N}}$— X⁻	References (Yield, %)
![benzimide structure] NCH₂— / CO \ NCH₂—	—$\overset{\oplus}{\text{N}}$(CH₃)₃ I⁻	180 (34)
	CH₂CH₂ CH₂ \ / CH₃$\overset{\oplus}{\text{N}}$ I⁻ / \ CH₂CH₂ CH₂CH₂	180 (33)
	CH₂CH₂ O \ / CH₃$\overset{\oplus}{\text{N}}$ I⁻ / \ CH₂CH₂ CH₂CH₂	180 (27)
![benzimidazole thione structure] NCH₂— / CS \ NCH₂—	—$\overset{\oplus}{\text{N}}$(CH₃)₃ I⁻	179 (88)

Note: References 382 to 537 are on pp. 266–269.

TABLE XXXI
N-ACYL- AND N-SULFONYL-IMINES

Imine Derivative	References (Yield, %)
Amides	
$HCON=CHC_6H_4OH\text{-}p$	297 (60)
$CH_3CON=CHC_6H_4OH\text{-}p$	297 (90)
$CH_3CON=C(C_6H_5)_2$	231 (70)
$CH_3CON=C[C_6H_4N(CH_3)_2\text{-}p]_2$	231, 490 (77)
$CH_3CON=C(C_{10}H_7\text{-}1)C_6H_5$	231
$CH_3CON=C(C_{10}H_7\text{-}2)C_6H_5$	231
$CH_3CON=C(C_{10}H_7\text{-}1)_2$	231

$CH_3CON=$

231

$CH_3CON=$

231, 491 (59), 492

$CH_3ClCON=CHCCl_2$	307
$CH_3ClCON=CHCCl_3$	307
$CH_3ClCON=C(C_6H_5)_2$	231
$C_6H_5CH_2CON=CHC_6H_4OH\text{-}o$	299
$C_6H_5CH_2CON=CHC_6H_4OH\text{-}m$	298 (40)
$C_6H_5CH_2CON=CHC_6H_4OH\text{-}p$	297 (80)
$C_2H_5CON=CHC_6H_4OH\text{-}o$	299
$C_2H_5CON=CHC_6H_4OH\text{-}m$	298 (27)
$C_2H_5CON=CHC_6H_4OH\text{-}p$	297 (83)
$C_2H_5CON=C(C_6H_5)_2$	231 (71)
$C_6H_5CON=C(C_6H_5)C_6H_4CH_3\text{-}o$	231
$n\text{-}C_3H_7CON=C(C_6H_5)_2$	231 (65)
$n\text{-}C_5H_{11}CON=CHC_6H_4OH\text{-}2\text{-}Cl\text{-}5$	271

Note: References 382 to 537 are on pp. 266–269.

TABLE XXXII

SYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
Amides		
$(HCONH)_2CH_2$	Amide, $(CH_2O)_3$	154 (32), 262, 494
	Amide, formalin, $(CH_3CO)_2O$	281 (21)
	Amide, hexamine	495 (53–83)
$(CH_3CONH)_2CH_2$	Amide, formalin, $(CH_3CO)_2O$	281 (70)
	Amide, formalin, CH_3CO_2H	154 (16), 279 (54)
	Amide, formalin, acid	246, 465
	Amide, $(CH_2O)_3$	494 (good)
	Amide, $(CH_2O)_x$	250 (62)
	Amide, hexamine, base	495 (good)
	RCN, CH_2O, HCl, H_2O, 300°	496
	RCN, 33% CH_2O, concd. HCl	497
$(CH_2ClCONH)_2CH_2$	$RCONHCH_2OH$, acid	11 (95), 465
$(CHCl_2CONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	465
$(CCl_3CONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	264
	$RCONHCH_2OH$, acid	264 (95), 465
$(CH_2BrCONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	465
$(CH_2ICONH)_2CH_2$	$RCONHCH_2OH$, acid	11, 465
$(NCSCH_2CONH)_2CH_2$	$(CH_2ClCONH)_2CH_2$, $KSCN$, C_2H_5OH	465
$[(C_2H_5)_2NCH_2CONH]_2CH_2$	$RCONHCH_2OH$, acid	153, 465
$(C_6H_5CH_2CONHCH_2CONH)_2CH_2$	$RCONHCH_2OH$, acid	70
	$RCONHCH_2OH$, acid	70
	Amide, formalin, acid	70
$(C_6H_5CONHCH_2CONH)_2CH_2$	$RCONHCH_2OH$, acid	70
	Amide, formalin, acid	70

CH₂=ClCH₂CONH₃CH₃	RCN, (CH₂O), 75 % H₂SO₄	4 (18)
(CH₂CH=ClCH₂CONH₃CH₃	RCN, (CH₂O), 90 % H₂SO₄	4 (9)
(C₄H₇CONH₃CH₃	Amide, formalin, acid	388 (88)
	RCONHCH₃OH, acid	79
(C₂H₅O₃CH₂CONH₃CH₃	RCN, (CH₂O), concl. H₂SO₄	4 (30), 261
H₃XCOCH₂CONH₃CH₃	RCN, (CH₂O), C₂H₅, H₂SO₄	4 (6)
[NCCH₂CONH₃CH₃	Amide, hexamine, HCONH(CH₃)₃, heat	465 (83)
C₄H₇CONH₃CH₃	Amide, formaldehyde, acid	465
	Amide, RCONHCH₃OH, heat	465
	RCONHCH₃OH, acid	153 (79)
	Amide, formalin, acid	153 (low)
	Amide, formaldehyde, acid	153 (40)
(CH₂ClCCONH₃CH₃	RCN, 33 % CH₂O, concl. HCl	153 (75)
(CH₂CCH₂CONH₃CH₃	CH₂=CHCN, CH₂O, HCl, H₂O, 400°	465
		467
CH₃brCH₂CONH₃CH₃	RCN, 37 % CH₂O, concl. H₂SO₄	405, 498
CH₂ClClCONH₃CH₃	Amide, (CH₂O)ₓ, HCl	499 (79)
CH₂ClCHCONH₃CH₃	RCN, 53 % CH₂O, HCl, 300°	499 (91)
CH₃brCHBrCONH₃CH₃	RCONHCH₃OH, acid	500
	RCN, 35 % CH₂O, HCl, 380°	253 (55)
[C₄H₇CH₂CONHCH(CH₃)₃CONH₃CH₃	RCONHCH₃OH, acid	500
	Amide, formalin, acid	79
[HO₂C(CH₂)₃CONH(CH₃)₃CONH₃CH₃	RCONHCH₃OH, acid	79
H₃XCO(CH₂)₃CONH(CH₃)₃CONH₃CH₃	Amide, (CH₂O)ₓ, acid	501
	Amide, hexamine, heat	502
[n-C₄H₇CONH₃CH₃	RCN, (CH₂O)ₓ, 85 % H₂SO₄	4 (40)
[CH₃brCHCH₂CH₃CONH₃CH₃	RCONHCH₃OH, HBr or H₂SO₄	253 (84)
	CH₃=C(CH₃)₃CONHCH₃OH, acid	253 (40)
	CH₃brCBr(CH₃)₃CONHCH₃OH, Br₂	253 (86)

TABLE XXXII—*Continued*

SYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
Amides (contd.)		
$(i\text{-}C_4H_9CONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	419 (85)
	$RCONHCH_2OH$, heat	419 (73)
$[(C_2H_5)_2CHCONH]_2CH_2$	Amide, $RCONHCH_2OH$, acid	153 (87)
$(n\text{-}C_7H_{15}CONH)_2CH_2$	RCN, $(CH_2O)_x$, acid	503 (good)
$(n\text{-}C_{11}H_{23}CONH)_2CH_2$	Amide, formalin, acid	217 (70), 222 (57)
	$RCOCl$, hexamino	504 (20)
	RCN, $(CH_2O)_x$, BF_3, CH_3CO_2H	503 (good)
$[CF_3(CH_2)_{11}CONH]_2CH_2$	$RCONHCH_2OH$, acid, $CH_3COC_3F_5$	217 (poor)
$(n\text{-}C_{15}H_{31}CONH)_2CH_2$	RCN, $(CH_2O)_x$, 90% H_2SO_4	503 (good)
$(n\text{-}C_{17}H_{35}CONH)_2CH_2$	RCN, $(CH_2O)_x$, 90% H_2SO_4	503 (100)
	$(RCONHCH_2)_2O$, acid	217 (100)
$RCONHCH_2N$⊕[pyridyl]	Cl⊖, acid	243 (99)
$(n\text{-}C_9H_{19}CONH)_2CH_2$	$RCONHCH_2OH$, acid	235
$(CH_2{=}CHCONH)_2CH_2$	RCN, $(CH_2O)_x$, 85% Et_2SO_4	4 (86)
	Amide, $(CH_2O)_x$, acid	254 (89), 505 (50)
	$RCONHCH_2OH$, acid	254 (87)
$(CH_2{=}CHCH_2CONH)_2CH_2$	RCN, formalin, concd. H_2SO_4	499 (58)
$[CH_2{=}C(CH_3)CONH]_2CH_2$	Amide, $RCONHCH_2OH$, acid	254 (80)
	$(RCONHCH_2)_2O$, acid, 60°	424 (81)
	$RCONHCH_2OH$, acid	254 (87)
	Amide, $(CH_2O)_x$, acid	254 (70), 505 (81)
$[(CH_3)_2C{=}CHCONH]_2CH_2$	$RCONHCH_2OH$, HCl, CCl_4	422 (95)

(C₆H₅CONHCH₂CH₂)		

Compound	Reagents	References
	RCONHCH₂OH, acid	10, 79, 132
	RCONHCH₂OR, heat	79
	RCONHCH₂OR', acid	79
	Amide, formalin, acid	10 (100), 246, 388
	Amide, hexamine, base	495 (good)
	RCN, (CH₂O)ₓ, 85–98% H₂SO₄	4 (90), 245, 500, 507
	Amide, RCONH(SO₄)Na, NaOC₂H₅, 200°	508 (84)
	RCOCl, hexamine, base	509
	(C₆H₅CONH)₂, Mg, (CH₃)₂S	246
(o-ClC₆H₄CONH₂CH₂	RCN, 32% CH₂O, concl. HBr	465, 497
(p-ClC₆H₄CONH₂CH₂	RCN, (CH₂O)ₓ, H₂SO₄, CHCl₃	4 (75)
(o-O₂NC₆H₄CONH₂CH₂	(RCONH)₂CH₂, H₂O, heat	221
(m-O₂NC₆H₄CONH₂CH₂	Amide, formalin, acid	221
(p-O₂NC₆H₄CONH₂CH₂	Amide, formalin, acid	221
(p-HOC₆H₄CONH₂CH₂	Amide, RCONH₂CH₂OH, acid	221
(p-CH₃OC₆H₄CONH₂CH₂	RCONHCH₂OH, acid	25 (100)
(p-CH₃C₆H₄CONH₂CH₂	RCN, (CH₂O)ₓ, 87% H₂SO₄	132 (100)
(p-CH₃)₂C₆H₄CONH₂CH₂	RCN, (CH₂O)ₓ, H₂SO₄, CHCl₃	4 (83)
(p-H₂C₆H₄C₆H₄CONH₂CH₂	Methyl ester, 5% NaOH, 100°	4 (50), 510 (84), 510 (95)
[N⟶CONH]₂CH₂	RCONH₂CH₂OH, 200°	430

Lactams, Thioamides, and Imides

Compound	Reagents	References
CH₃CO / N / CH₂ structure	Lactam, formalin, acid	247, 248

Note: References 382 to 537 are on pp. 260–269.

TABLE XXXII—*Continued*

SYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
Amides (contd.)		
$(i-C_3H_6CONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	419 (85)
	$RCONHCH_2OH$, heat	419 (73)
	Amide, $RCONHCH_2OH$, acid	153 (97)
$[(C_3H_5)_2CHCONH]_2CH_2$	RCN, $(CH_2O)_n$, acid	503 (good)
$(n-C_7H_{16}CONH)_2CH_2$	Amide, formalin, acid	217 (70), 222 (57)
$(n-C_{11}H_{23}CONH)_2CH_2$	RCOCl, hexamine	504 (20)
	RCN, $(CH_2O)_n$, BF_3, CH_3CO_2H	503 (good)
	$RCONHCH_2OH$, acid, $CH_3COC_3H_5$	217 (poor)
$[C_2H_5(CH_2)_4CONH]_2CH_2$	RCN, $(CH_2O)_n$, 80 % H_2SO_4	503 (good)
$(n-C_{16}H_{31}CONH)_2CH_2$	RCN, $(CH_2O)_n$, 80 % H_2SO_4	503 (100)
$(n-C_{17}H_{35}CONH)_2CH_2$	RCN, $(CH_2O)_n$, 80 % H_2SO_4	217 (100)
	$(RCONHCH_2)_2O$, acid	
	ClC, acid	243 (99)
$(n-C_{21}H_{43}CONH)_2CH_2$	$RCONHCH_2OH$, acid	235
$[CH_2\ CHCONH)_2CH_2$	RCN, $(CH_2O)_n$, 85 % H_2SO_4	4 (80)
	Amide, $(CH_2O)_n$, acid	254 (80), 505 (50)
	$RCONHCH_2OH$, acid	254 (97)
$[CH_2\ CHCH_2CONH)_2CH_2$	RCN, formalin, concd. H_2SO_4	499 (58)
$[C(CH_3)_3CONH)_2CH_2$	Amide, $RCONHCH_2OH$, acid	254 (80)
	$(RCONHCH_2)_2O$, acid, 80°	424 (81)
	$RCONHCH_2OH$, acid	254 (97)
	Amide, $(CH_2O)_n$, acid	254 (70), 505 (81)
$[(CH_3)_3C\ CHCONH]_2CH_2$	$RCONHCH_2OH$, HCl, CCl_4	422 (66)

(C₆H₅CONH)₂CH₂	RCONHCH₂OH, acid	10, 79, 132
	RCONHCH₂OR', heat	79
	RCONHCH₂OR', acid	79
	Amide, hexamine, base	10 (100), 240, 388
	RCN, (CH₂O)ₙ, 85–98% H₂SO₄	495 (good)
	Amide, RCONHCH₂SO₃Na, NaOC₂H₅, 200°	4 (90), 245, 506, 507
	RCOCl, hexamine, base	508 (84)
	(C₆H₅CONH)₂Hg, (CH₃)₂S₂	509
(o-ClC₆H₄CONH)₂CH₂	RCN, 33% CH₂O, concd. HBr	246
(p-ClC₆H₄CONH)₂CH₂	RCN, (CH₂O)ₙ, H₂SO₄, CHCl₃	465, 497
(o-O₂NC₆H₄CONH)₂CH₂	(RCONHCH₂)₂O, heat	4 (75)
(m-O₂NC₆H₄CONH)₂CH₂	Amide, formalin, acid	221
(p-O₂NC₆H₄CONH)₂CH₂	Amide, formalin, base	221
(o-HOC₆H₄CONH)₂CH₂	Amide, formalin, acid	221
(p-HOC₆H₄CONH)₂CH₂	Amide, RCONHCH₂OH, acid	25 (100)
(p-CH₃C₆H₄CONH)₂CH₂	RCONHCH₂OH, acid	132 (100)
(p-C₂H₅OC₆H₄CONH)₂CH₂	RCN, (CH₂O)ₙ, 85% H₂SO₄	4 (83)
(p-HO₂CC₆H₄CONH)₂CH₂	RCN, CH₂O, H₂SO₄, CHCl₃	4 (50), 510 (84)
	Methyl ester, 5% NaOH, 100°	510 (95)

Lactams, Thioamides, and Imides

[pyridine ring]–CONH–CH₃ (structure)	RCONHCH₂OH, 200°	430
CH₃CO–N(CH₂…)₂ (structure)	Lactam, formalin, acid	247, 248

TABLE XXXII—*Continued*

·SYMMETRICAL, N,N′-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
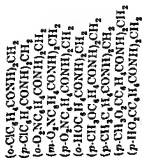
N,N′-Methylene-*bis* Derivative	Method	References (Yield, %)
Lactams, Thioamides, and Imides (contd.)		
$(CH_3CONH)_2CH_2$	$CH_3CONH)_2CH_2$, P_2S_5	246, 465
$[o\text{-}C_6H_4(CO)_2N]_2CH_2$	$o\text{-}C_6H_4(CN)_2$, $(CH_2O)_x$,	4 (20)
	H_2SO_4, $CHCl_3$	
	$o\text{-}C_6H_4(CO)_2NK$,	81 (48)
	$o\text{-}C_6H_4(CO)_2NCH_2N(CH_3)_3$ $I^⊖$	256
	$o\text{-}C_6H_4(CO)_2NK$, CH_2I_2	502
	$o\text{-}C_6H_4(CO)_2NH$, hexamine, heat	220 (low)
	$o\text{-}C_6H_4(CO)_2NCH_2N(CH_3)_2$, $100°$	
$\left[\begin{array}{c} CO \\ \\ SO_2 \end{array} \right]N{-}CH_2\Big]_2$	Imide, formalin, acid	511 (low)
Carbamyl Compounds		
$(C_2H_5O_2CNH)_2CH_2$	$C_2H_5O_2CNHCH_2OH$, acid	153
	$C_2H_5O_2CNH_2$, formalin, acid	250 (85), 251
	CH_3NCO, $CH_2(OCH_3)_2$	258
$(CH_3O_2CNCH_2)_2CH_2$	$CH_3O_2CNHCH_3$, formalin, acid	250 (fair), 251
$(C_2H_5O_2CNCH_3)_2CH_2$	$RO_2CNHCH_2CO_2C_2H_5$, $(CH_2O)_x$, acid, C_6H_6	344 (65)
$(C_6H_5CH_2O_2CNCH_2CO_2H)_2CH_2$	CH_3NCO, $CH_2(SC_4H_9\text{-}n)_2$	258
$[n\text{-}C_4H_9OC(=S)NCH_3]_2CH_2$	$H_2NCONHCH_2OH$, acid	146, 147
$(H_2NCONH)_2CH_2$	$CO(NH_2)_2$, formalin, acid	146, 147, 210 (17)
$(CH_3NHCONH)_2CH_2$	$CH_3NHCONH_2$, formalin, acid	210 (74), 483
$(C_2H_5NHCONH)_2CH_2$	$C_2H_5NHCONH_2$, formalin, acid	153

(CH₃NHCONHCH₂)₂CH₂ [(CH₃)₂NCONH]₂CH₂ (C₂H₅NHCONH)₂CH₂ p-CH₃C₆H₄NHCONH)₂CH₂	CO(NHCH₃)₂, formalin, acid (CH₃)₂NCONH₂, formalin, acid (H₂NCONH)₂CH₂, C₂H₅NHCONH₂ p-CH₃C₆H₄NHCONH₂, formalin, acid	153 153 475 (60) 55
CHCO [NCONH]₂ CHCO	NCONH₂, (CH₂O)ₓ, conc. H₂SO₄	511a (22)
(H₂NCSNH)₂CH₂ (H₂NCSNHCH₂)₂CH₂	CS(NH₂)₂, formalin, acid CS(NHCH₃)₂, formalin, acid	265 512
CONH [CO CH₂]₂ CH₂N	Hydantoin, formalin, acid Hydantoin, (CH₂O)ₓ, conc. HCl Hydantoin, formalin, H₂SO₄, CH₃CO₂H	185 (42) 252 (87) 290 (97)
CONH [CO CH₂]₂ n-C₃H₇CHN	n-Propylhydantoin, formalin, ZnCl₂, conc. HCl	289 (54)
CONH [CO CH₂]₂ i-C₃H₇CHN	i-Propylhydantoin, aq. CH₂O, ZnCl₂, conc. HCl i-Propylhydantoin, formalin, H₂SO₄, CH₃CO₂H	289 (64) 290 (60)

TABLE XXXII—*Continued*

SYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

Carbamyl Compounds (contd.)

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
$\left[\begin{array}{c}\text{CONH}\\\quad\quad\text{CO} \quad \text{CH}_2\\(\text{CH}_3)_2\text{C}\text{—N}\end{array}\right]_2$	Dimethylhydantoin, aq. CH$_2$O, HCl	252 (96)
$\left[\begin{array}{c}\text{CONCl}\\\quad\quad\text{CO} \quad \text{CH}_2\\(\text{CH}_3)_2\text{C}\text{—N}\end{array}\right]_2$	Dimethylhydantoin, formalin, ZnCl$_2$, concd. HCl	289 (81)
$\left[\begin{array}{c}\text{OC—NH}\\\quad\quad\text{CO} \quad \text{CH}_2\\\text{C}_2\text{H}_5\text{C}(\text{CH}_3)\text{N}\text{—}\end{array}\right]_2$	Methylenebisdimethylhydantoin, Cl$_2$	288 (92)
$\left[\begin{array}{c}\text{OC—NH}\\\quad\quad\text{CO} \quad \text{CH}_2\\\text{C}_2\text{H}_5\text{C}(\text{CH}_3)\text{N}\text{—}\end{array}\right]_2$	Methylethylhydantoin, formalin, ZnCl$_2$, concd. HCl	289 (82)
$\left[\begin{array}{c}\text{OC—NH}\\\quad\quad\text{CO} \quad \text{CH}_2\\i\text{-C}_4\text{H}_9\text{C}(\text{CH}_3)\text{N}\text{—}\end{array}\right]_2$	Methyl-*i*-butylhydantoin, formalin, ZnCl$_2$, concd. HCl	289 (67)
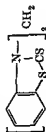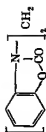
3-Chloromethyl-2-benzoxazolone, 2-benzoxazolone   194 (60)

I_2, 200°   318 (100)

Amide, formaldehyde, acid	465
Amide, formalin, K_2CO_3	85 (70)
$C_6H_5SO_2NHCH_2OH$, C_2H_6, heat	156
Amide, formalin, C_2H_6	156
Amide, formalin, K_2CO_3	85 (80)
$ArSO_2NHCH_2OH$, C_6H_6, heat	156
Amide, $(CH_2O)_x$, HCl	156
Amide, $(CH_2O)_x$, HCl	156
Amide, $(CH_2O)_x$, HCl	156
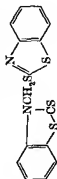
Sulfonamides

$(C_6H_5ClSO_2NH_2CH_2$
$(C_4H_5SO_2NH_2CH_2)_2$

$(o\text{-}CH_2C_6H_4SO_2NH_2CH_2$
$(p\text{-}CH_3C_6H_4SO_2NH_2CH_2$

$(p\text{-}CH_3C_6H_4SO_2N(CH_2)_2CH_2$
$(p\text{-}CH_3C_6H_4SO_2NC_6H_4CH_2$

Note: References 382 to 537 are on pp. 266–269.

TABLE XXXIII

UNSYMMETRICAL N,N'-METHYLENE-bis DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
Amides		
HO_2CCH_2CONH — CH_2 — $CH_2ClCONH$	$CH_2ClCONHCH_2OH$, $CH_2(CO_2H)CONH_2$, acid	465
$(C_2H_5)_2NCH_2CONH$ — CH_2 — $(C_2H_5)_2CHCONH$	$RCONHCH_2OH$, $(C_2H_5)_2NCH_2CONH_2$, concd. H_2SO_4	153
$n\text{-}C_{17}H_{35}CONH$ — CH_2 — $n\text{-}C_{17}H_{35}CONH$	$CH_2{=}CHCONH$, $n\text{-}C_{14}H_{29}SH$ / $n\text{-}C_{17}H_{35}CONH$	217
$n\text{-}C_{11}H_{23}S(CH_2)_2CONH$ — CH_2 — $n\text{-}C_{17}H_{35}CONH$		
NaO_3SCH_2CONH	$CH_2(SO_3Na)CONHCH_2OH$, $RCONH_2$, CH_3CO_2H, 100°	249

$n\text{-}C_7H_{15}CONCH_3$ 　$|$ 　CH_2 NaO_2SCH_2CONH $CH_2{=}CHCONH$	$CH_3(SO_2Na)CONHCH_2OH$, $RCONHCH_3$, CH_3CO_2H, $100°$	249
CH_2CONH $CH_2{=}CHCONH$	$CH_3CONHCH_2OH$, $CH_2{=}CHCONH_2$, acid, 30–$50°$	217 (69)
CH_2 CH_2CONH $CH_2{=}CHCONH$	$RCONHCH_2OH$, $CH_2{=}CHCONH_2$, acid, 50–$55°$	217 (85)
$n\text{-}C_9H_{19}CONH$ 　CH_2 $CH_2{=}CHCONH$	$RCONHCH_2OH$, $CH_2{=}CHCONH_2$, acid, 50–$55°$	217 (81)
$n\text{-}C_{11}H_{23}CONH$ 　CH_2 $CH_2{=}CHCONH$	$RCONHCH_2OH$, $CH_2{=}CHCONH_2$, acid, 50–$55°$	217 (85)
$n\text{-}C_{13}H_{27}CONH$	$RCONHCH_2OH$, $CH_2{=}CHCONH_2$, acid, 50–$55°$	217 (87)

Note: References 392 to 537 are on pp. 266–269.

TABLE XXXIII—*Continued*

UNSYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
Amides (contd.)		

CH_2—$C(CH_3)CONH$
    |
   CH_2
    |
n-$C_{17}H_{35}CONH$
	$RCONHCH_2OH$, CH_2=$C(CH_3)CONH_2$, acid, 50–55°	217 (81)

CH_2=$CHCONH$
    |
   CH_2
    |
CH_2=$C(CH_3)CONH$
	$RCONHCH_2OH$, CH_2=$C(CH_3)CONH_2$, acid, 80°	513 (63)

C_6H_5CONH
    |
   CH_2
    |
CH_3CONH
	$(C_6H_5CONH)_2CH_2$, $(CF_3CONH)_2CH_2$, 270°	514 (5)

$CH_2ClCONH$
    |
   CH_2
    |
C_6H_5CONH
	$CH_2ClCONHCH_2OH$, $C_6H_5CONH_2$, acid	465

C_6H_5CONH
    |
   CH_2
    |
$C_2H_5O_2C(CH_3)CH(CO_2C_2H_5)CONH$
	$C_6H_5CONHCH_2OH$, concd. H_2SO_4, $C_2H_5O_2C(CH_3)_4CH(CO_2C_2H_5)CN$	84, 119 (91)

C₆H₅CONH CH₃	RCONHCH₂OH, C₆H₅CONH₂, HCl, dioxane	249
n-C₇H₁₅CONH CH₃	C₆H₅CONHCH₂OH, CH₂=CHCN, 96% H₂SO₄, 30°	255 (60)
CH₂=CHCONH CH₃		
C₆H₅CONH CH₃	ArCONHCH₂OH, C₆H₅CONH₂, acid	25 (88)
o-HOC₆H₄CONH CH₃		

Lactams and Imides

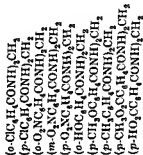|		
NCH₂NHCOC(CH₃)=CH₂ (pyrrolidinone)	Lactam, RCONHCH₂OCH₃, NaOC₂H₅, 130–170°	477
NCH₂NHCOC(CH₃)=CH₂ (azepanone)	Lactam, RCONHCH₂OCH₃, NaOC₂H₅, 130–170°	477

Note: References 382 to 537 are on pp. 286–299.

TABLE XXXIII—Continued

UNSYMMETRICAL N,N'-METHYLENE-bis DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
Lactams and Imides (contd.)		
o-$C_6H_4(CO)_2$N—CH_2NHCOC_6H_5	C_6H_5CONHCH_2N(CH_3)$_2$, isatin, NaOH, C_6H_5CH_3, heat	257 (75)
o-$C_6H_4(CO)_2$NCH_2NHCOCH_3	o-$C_6H_4(CO)_2$NCH_2OH, CH_3CN, concd. H_2SO_4, 80°	84 (83)
o-$C_6H_4(CO)_2$N—CH_2	o-$C_6H_4(CO)_2$NCH_2OH, NCCH_2CO_2H, concd. H_2SO_4, 45°	84 (91)
o-$C_6H_4(CO)_2$NCH_2NHCOC(CH_3)=CH_2 HO$_2$CCH_2CONH	Imide, RCONHCH_2OCH_3, NaOC$_2H_5$, 130–170° Imide, C_6H_5CONHCH_2SO$_3$Na, NaOC$_2H_5$, 200° Imide, C_6H_5CONHCH_2N(CH_3)$_2$, NaOH, C_6H_5CH_3 o-$C_6H_4(CO)_2$NCH_2OH, C_6H_5CN, concd. H_2SO_4, 80°	477 (92) 508 (51) 257 (68) 84 (77)
Carbamyl Compounds		
$C_2H_5O_2$CNH—CH_2—CH_2ClCONH	CH_2ClCONHCH_2CONHNH_2, HNO$_2$, C_2H_5OH	259 (37), 465
$C_2H_5O_2$CNH—CH_2—CH_2BrCONH	CH_2BrCONHCH_2CONHNH_2, HNO$_2$, C_2H_5OH	259 (35)

$C_2H_5O_2CNH$	$CH_2CONHCH_2CON_3$, C_2H_5OH	250 (94)
	CO—NCH_2CON_3	
CH_3CONH	CO, C_2H_5OH	187 (70)
CO—$NC_2H_5C(C_2H_5)NH$		
$C_2H_5C(C_2H_5)NH$		
	NCH_2NHAr, CH_3COCl, pyridine	260 (82)
	NCH_2NHAr, CH_3COCl, pyridine	200 (87)
	NCH_2NHAr, CH_3COCl, pyridine	200 (80)
	NCH_2NHAr, CH_3COCl, pyridine	200 (78)
	NCH_2Cl, saccharin	178 (48)

Note: References 282 to 537 are on pp. 295–299.

TABLE XXXIII—*Continued*

UNSYMMETRICAL, N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, IMIDES,
CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-*bis* Derivative	Method	References (Yield, %)
Carbamyl Compounds (contd.)		
(bis structure)	(structure: NCH$_2$Cl · N Na$^{\oplus}$)	178 (60)
Sulfonamides and Sulfamyl Compounds		
C$_6$H$_5$SO$_2$NH—CH$_2$—C$_6$H$_5$CONH	C$_6$H$_5$SO$_2$NHCH$_2$OH, C$_6$H$_5$CONH$_2$, xylene	82 (11)
	C$_6$H$_5$CONHCH$_2$OH, C$_6$H$_5$SO$_2$NH$_2$, NaOH, C$_6$H$_5$CH$_3$	257 (86)
p-CH$_3$C$_6$H$_4$SO$_2$NCH$_3$—CH$_2$—C$_6$H$_5$CONH	ArSO$_2$NHCH$_3$, C$_6$H$_5$CONHCH$_2$N(CH$_3$)$_2$, NaOH, C$_6$H$_5$CH$_3$	257 (70)
HO$_3$SNH—CH$_2$—C$_6$H$_5$CONH	C$_6$H$_5$CONH$_2$, H$_2$NSO$_3$H, CH$_2$O, 99% H$_2$SO$_4$, 70°	515 (20)

Note: References 382 to 537 are on pp. 286–289.

TABLE XXXIV

SYMMETRICAL N,N'-ALKYLIDENE-*bis* AND N,N'-ARYLIDENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides			
Formamide and			
Acetaldehyde	$(CH_3CO)_2O$, heat	4	281
β-Phenylpropionaldehyde	No solvent, heat	0	516
Heptanal	Heat alone, or in $(CH_3CO)_2O$, or in pyridine	0	517
Cinnamaldehyde	$(CH_3CO)_2O$, heat	28	281
Benzaldehyde	$(CH_3CO)_2O$, heat	56	281
	No solvent, heat	Poor	287, 518
o-Chlorobenzaldehyde	No solvent, heat	Poor	518
o-Nitrobenzaldehyde	Pyridine	40	274
m-Nitrobenzaldehyde	No solvent, heat	40	274
p-Nitrobenzaldehyde	No solvent, heat	67	269
3,5-Dichlorosalicylaldehyde	H_2O, acid	0	269
o-Anisaldehyde	No solvent, heat	—	271
m-Anisaldehyde	No solvent, heat	0	296a
p-Anisaldehyde	No solvent, heat	25	296a
	$(CH_3CO)_2O$, heat	0	296a
Veratraldehyde	No solvent, heat	0	296a
o-Acetylvanillin	$(CH_3CO)_2O$, heat	20	281
Piperonal	$(CH_3CO)_2O$, heat	21	281
6-Nitropiperonal	No solvent, heat	0	519
p-$(CH_3)_2NC_6H_4CHO$	No solvent, heat	0	520
m-Tolualdehyde	$(CH_3CO)_2O$, heat	18	281
	Pyridine	48	273

Note. References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued

SYMMETRICAL N,N'-ALKYLIDENE-bis AND N,N'-ARYLIDENE-bis DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
Formamide (contd.) and			
p-Toluαldehyde	Pyridine	<50	276
	No solvent, heat	0	276
1-Naphthaldehyde	(CH₃CO)₂O, heat	51	282
Acetamide and			
Acetaldehyde	(CH₃CO)₂O, heat	66	281
	CH₃CO₂H, heat	38, 44	154, 279
	No solvent, heat	—	521
	C₂H₅OCH=CH₂, heat, acid	82	233
	CH₃CHO, CH₃CN, HCl, H₂O, 300ᶜ	—	496
Chloral	CCl₃CHO, CH₃CN, concl. H₂SO₄	—	261, 295
Propionaldehyde	(CH₃CO)₂O, heat	62	281
	CH₃CO₂H, heat	35, 7	154, 279
	C₆H₆, heat	48	283
	Pyridine, heat	11	452
β-Phenylpropionaldehyde	Pyridine	9	516
n-Butyraldehyde	No solvent, heat	20	516
	(CH₃CO)₂O, heat	76	281
	CH₃CO₂H, heat	11	279
	C₆H₆, heat	49	283
Isovaleraldehyde	(CH₃CO)₂O, heat	47	281
	CH₃CO₂H, heat	26	279
Heptanal	CH₃CO₂H, heat	6	279
	No solvent, heat	—	517
Cyclohexanecarboxaldehyde	(CH₃CO)₂O, heat	54	280

Cinnamaldehyde	(CH₃CO)₂O, heat	47	281
	C₆H₆, heat	33	283
	Pyridine	15	275
Benzaldehyde	No solvent, heat	52	275
	(CH₃CO)₂O, H₂SO₄, heat	40	85
	(CH₃CO)₂O, heat	71	281
	CH₃CO₂H, heat	17	154
	CH₃CO₂H, heat	48	279
	C₆H₆, heat	72	283
	No solvent, heat	49	284
o-Chlorobenzaldehyde	No solvent, heat	—	287, 518, 522, 523
o-Nitrobenzaldehyde	(CH₃CO)₂O, heat	Good	518
	H₂O, acid	67	281
	Pyridine	—	278
m-Nitrobenzaldehyde	No solvent, heat	48	274
	(CH₃CO)₂O, heat	48	274
	C₆H₆, heat	74	281
	H₂O, acid	44	283
p-Nitrobenzaldehyde	No solvent, heat	—	278
	(CH₃CO)₂O, heat	60	269
Salicylaldehyde	No solvent, heat	61	281
5-Chlorosalicylaldehyde	C₆H₆, heat	54	269
3,5-Dichlorosalicylaldehyde	No solvent, heat	Poor	283
o-Anisaldehyde	No solvent, heat	53	271
m-Anisaldehyde	No solvent, heat	—	271
p-Anisaldehyde	No solvent, heat	40–60	296a
	C₆H₆, heat	40–60	296a
p-Animaldehyde	No solvent, heat	84	283
	No solvent, heat	40–60	296a, 524

Note: References 392 to 537 are on pp. 265-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—*Continued*

SYMMETRICAL N,N'-ALKYLIDENE-*bis* AND N,N'-ARYLIDENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
Acetamide (*contd.*) and			
Valeraldehyde	$(CH_3CO)_2O$, heat	52	112, 281
	$(CH_3CO)_2O$, heat	64	112, 281
O-Acetylvanillin	$(CH_3CO)_2O$, heat	43	281
Piperonal	$(CH_3CO)_2O$, heat	43	283
	C_6H_6, heat	42	519
	No solvent, heat	29	525
α-Bromopiperonal	No solvent, heat	61	520
α-Nitropiperonal	No solvent, heat	30	281
p-$(CH_3)_2NC_6H_4CHO$	$(CH_3CO)_2O$, heat	43	273
m-Tolualdehyde	Pyridine	65	281
p-Tolualdehyde	$(CH_3CO)_2O$, heat	<50	276
	Pyridine or heat alone	51	281
Cinnamaldehyde	$(CH_3CO)_2O$, heat	63	282
1-Naphthaldehyde	$(CH_3CO)_2O$, heat	36	282
2-Naphthaldehyde	$(CH_3CO)_2O$, heat	65	282
9-Anthraldehyde	$(CH_3CO)_2O$, heat	80	282
1-Pyrenecarboxaldehyde	$(CH_3CO)_2O$, heat	69	281
2-Furaldehyde	$(CH_3CO)_2O$, heat	67	283
	C_6H_6, heat	51	284
	No solvent, heat	74	280, 282
2-Thiophenecarboxaldehyde	$(CH_3CO)_2O$, heat	0	280
2-Pyrrolecarboxaldehyde	$(CH_3CO)_2O$, heat	0	280
Picolinaldehyde	No solvent, heat	89	280
Nicotinaldehyde	No solvent, heat	0	280
Isonicotinaldehyde	No solvent, heat	0	280
3-Indolecarboxaldehyde	$(CH_3CO)_2O$, heat	71	280

HO₂C(CH₂)₂CHO	HO₂C(CH₂)₂COCO₂H, heat (−CO₂)	25	292
Pyruvic acid	Heat in vacuum or CH₃CN, CH₃COCO₂H, H₂SO₄		291
Benzoylformic acid	Heat in vacuum	55	292
Acetaldehyde and p-Toluraldehyde	Pyridine or heat alone	<60	270
Fluoroacetamide and o-Chlorobenzaldehyde	(CH₃CO)₂O, heat		465
Chloroacetamide and Acetaldehyde	No solvent, H₂SO₄, heat		465
Phenylacetaldehyde	CH₃CO₂H, H₂SO₄		465
Propionaldehyde	CH₃CO₂H, heat		465
CH₃SCH₂CH₂CHO	CH₃CO₂H, H₂SO₄		465
Butyraldehyde	CH₃CO₂H, heat		465
Isobutyraldehyde	CH₃CO₂H, H₂SO₄		465
Valeraldehyde	CH₃CO₂H, H₂SO₄		465
Heptanal	CH₃CO₂H, H₂SO₄		465
⬡CHO	CH₃CO₂H, H₂SO₄		465
⬡(CH₃)CHO	CH₃CO₂H, H₂SO₄		465
Crotonaldehyde	CH₃CO₂H, H₂SO₄		405
Cinnamaldehyde	(CH₃CO)₂O, heat		405
Benzaldehyde	(CH₃CO)₂O, HCl, heat	78	85
	CH₃CO₂H, heat		405

Note: References 382 to 537 are on pp. 206–269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued

SYMMETRICAL N,N'-ALKYLIDENE-bis AND N,N'-ARYLIDENE-bis DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
Chloroacetamide (contd.) and			
o-Fluorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
o-Chlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
m-Chlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
p-Chlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
2,4-Dichlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
2,5-Dichlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
2,6-Dichlorobenzaldehyde	CH_3CO_2H, $ZnCl_2$, heat	—	465
2,6-Dichlorobenzaldehyde	$(CH_3CO)_2O$, heat	—	465
o-Bromobenzaldehyde	CH_3CO_2H, $ZnCl_2$, heat	—	307
o-Nitrobenzaldehyde	No solvent, heat	—	307
m-Nitrobenzaldehyde	No solvent, heat	—	465
p-Nitrobenzaldehyde	$(CH_3CO)_2O$, heat	—	307
2-Chloro-5-nitrobenzaldehyde	No solvent, heat	—	465
o-Acetoxybenzaldehyde	$(CH_3CO)_2O$, heat	—	465
o-Acetoxybenzaldehyde	CH_3CO_2H, heat	—	465
p-Acetoxybenzaldehyde	$(CH_3CO)_2O$, heat	—	465
o-Anisaldehyde	CH_3CO_2H, heat	—	465
p-Anisaldehyde	CH_3CO_2H, heat	—	465
o-$HO_2CCH_2OC_6H_4CHO$	No solvent, heat	—	307
Piperonal	$(CH_3CO)_2O$, heat	—	465
p-$(CH_3)_2NC_6H_4CHO$	CH_3CO_2H, heat	—	465
p-$CH_3CONHC_6H_4CHO$	CH_3CO_2H, heat	—	465
o-NCC_6H_4CHO	$(CH_3CO)_2O$, heat	—	465

o-Tolualdehyde	(CH₃CO)₂O, heat	—	465
m-Tolualdehyde	No solvent, heat	—	307
p-Tolualdehyde	No solvent, heat	—	307
3-Cl-4-CH₃C₆H₃CHO	CH₃CO₂H, heat	—	465
p-C₆H₄(CHO)₂ (*bis* epd.)	CH₃CO₂H, heat	—	465
1-Naphthaldehyde	(CH₃CO)₂O, heat	—	465
5-Nitro-2-furaldehyde	(CH₃CO)₂O, heat	—	465
2-Thiophenecarboxaldehyde	No solvent, heat	—	307
(structure: CHO, S)	(CH₃CO)₂O, heat	—	465
(structure: CHO, N-COCH₃)	(CH₃CO)₂O, heat	—	465
Pyruvic acid	Heat, in vacuum	—	291, 465
Dichloroacetamide and o-Chlorobenzaldehyde	(CH₃CO)₂O, heat	—	465
Pyruvic acid	Heat, in vacuum	—	291
Trichloroacetamide and Benzaldehyde	Heat alone or in (CH₃CO)₂O	0	85
Bromoacetamide and o-Chlorobenzaldehyde			
Iodoacetamide and o-Chlorobenzaldehyde	(CH₃CO)₂O, heat	—	465
o-Chlorobenzaldehyde	o-ClC₆H₄CH(NHCOCH₂Cl)₂, KI, CH₃OH	—	465

Note: References 382 to 537 are on pp. 266–269.

* Excerpt when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—*Continued*

SYMMETRICAL N,N'-ALKYLIDENE-*bis* AND N,N'-ARYLIDENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
$(C_2H_5)_2NCH_2CONH_2$ and o-Chlorobenzaldehyde	o-ClC$_6$H$_4$CH(NHCOCH$_2$Cl)$_2$, (C$_2$H$_5$)$_2$NH	—	465
N$_3$CH$_2$CONH$_2$ and o-Chlorobenzaldehyde	o-ClC$_6$H$_4$CH(NHCOCH$_2$Cl)$_2$, NaN$_3$, CH$_3$OH	—	465
Phenylacetamide and Acetaldehyde	No solvent, heat, acid	—	526
	n-C$_4$H$_9$OCH=CH$_2$, heat, acid	81	233
	CH$_3$CHO, C$_6$H$_5$CH$_2$CN, concd. HCl	—	527
	CCl$_3$CHO, C$_6$H$_5$CH$_2$CN, concd. H$_2$SO$_4$	18	201
Chloral	Pyridine or heat alone	Good	275
Cinnamaldehyde	No solvent, heat	97	518
o-Chlorobenzaldehyde	No solvent, heat	97	269
m-Nitrobenzaldehyde	No solvent, heat	35	269
p-Nitrobenzaldehyde	No solvent, heat	86	528
5-Chlorosalicylaldehyde	No solvent, heat	40–60	528
3,5-Dichlorosalicylaldehyde	No solvent, heat	40–60	296a
o-Anisaldehyde	No solvent, heat	40–60	296a
m-Anisaldehyde	No solvent, heat	54	296a
p-Anisaldehyde	No solvent, heat	10	519
Piperonal	No solvent, heat	48	520
o-Nitropiperonal	No solvent, heat		
m-Tolualdehyde	Pyridine		273

Propionamide and			
β-Phenylpropionaldehyde	No solvent, heat	20	516
Heptanal	No solvent, heat	—	517
Cinnamaldehyde	No solvent, heat	51	275
Benzaldehyde	No solvent, heat	45	284, 518
o-Chlorobenzaldehyde	No solvent, heat	Good	518
m-Nitrobenzaldehyde	Pyridine or heat alone	49	274
o-Nitrobenzaldehyde	No solvent, heat	67	269
p-Nitrobenzaldehyde	No solvent, heat	54	269
5-Chlorosalicylaldehyde	No solvent, heat	—	271
3,5-Dichlorosalicylaldehyde	No solvent, heat	—	271
o-Anisaldehyde	No solvent, heat	40–60	206a
m-Anisaldehyde	No solvent, heat	40–60	206a
p-Anisaldehyde	No solvent, heat	40–60	206a
Piperonal	No solvent, heat	36	519
6-Bromopiperonal	No solvent, heat	32	525
6-Nitropiperonal	No solvent, heat	15	529
p-Tolualdehyde	Pyridine	36	273
2-Furaldehyde	Pyridine or heat alone	50	276
	No solvent, heat	46	284
$CH_2ClCH_2CONH_2$ and			
Acetaldehyde	CH_3CHO, CH_2ClCH_2CN, HCl, H_2O, 300°		465, 490, 500
Benzaldehyde	CH_3CO_2H, heat		465
$CH_2ClCHClCONH_2$ and			
Acetaldehyde	CH_3CHO, $CH_2ClCHClCN$, HCl, H_2O, 250°		496, 500
$CH_2ClCHClCONH_2$ and			
Acetaldehyde	CH_3CHO, $CH_3CHClCClCN$, HCl, H_2O, 250°		500
	C_2H_5CHO, $CH_2ClCClCN$, HCl, H_2O, 380°		
Benzaldehyde			465, 500

Note: References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued

SYMMETRICAL N,N'-ALKYLIDENE-bis AND N,N'-ARYLIDENE-bis DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
CH₃BrCH₂CONH₂ and Acetaldehyde	CH₃CHO, CH₂BrCH₂CN, HCl, H₂O, heat	—	500
CH₃BrCHBrCONH₂ and Acetaldehyde	CH₃CHO, CH₂BrCHBrCN, HCl, H₂O, 380°	—	465, 500
Butyramide and			
Chloral	CCl₃CHO, RCN, 96 % H₂SO₄	67	4
β-Phenylpropionaldehyde	No solvent, heat	22	516
Butyraldehyde	RCHO, RCN, 96 % H₂SO₄	19	4
Heptanal	Heat alone, or in (CH₃CO)₂O, or in pyridine	0	517
Benzaldehyde	No solvent, heat	Good	518, 523
Benzaldehyde	No solvent, heat	Good	518
o-Chlorobenzaldehyde	No solvent, heat	65	274
o-Nitrobenzaldehyde	No solvent, heat	84	269
m-Nitrobenzaldehyde	No solvent, heat	72	269
p-Nitrobenzaldehyde	No solvent, heat	—	271
5-Chlorosalicylaldehyde	No solvent, heat	—	271
3,5-Dichlorosalicylaldehyde	No solvent, heat	55	519
Piperonal	No solvent, heat	57	520
6-Nitropiperonal	No solvent, heat	39	273
m-Tolualdehyde	Pyridine		
HO₂C(CH₂)₄CONH₂ and Acetaldehyde	CH₃CHO, HO₂C(CH₂)₄CN, concd. HCl	—	497
	CH₃CHO, HO₂C(CH₂)₄CN, HCl, H₂O, 250°	—	490, 500

|			
Heptanamide and			
β-Phenylpropionaldehyde	No solvent, heat	40	516
Heptanal	Heat alone, or in (CH₃CO)₂O, or in pyridine	0	517
Cinnamaldehyde	No solvent, heat	41	530
Benzaldehyde	No solvent, heat	Good	518
o-Chlorobenzaldehyde	No solvent, heat	Good	518
o-Nitrobenzaldehyde	No solvent, heat	100	274
m-Nitrobenzaldehyde	No solvent, heat	97	269
p-Nitrobenzaldehyde	No solvent, heat	97	269
3,5-Dichlorosalicylaldehyde	No solvent, heat	—	271
Piperonal	No solvent, heat	77	519
6-Bromopiperonal	No solvent, heat	36	525
6-Nitropiperonal	No solvent, heat	55	520
m-Toluablehyde	Pyridine or heat alone	<40	273
Cyclohexanecarboxamide and			
Acetaldehyde	(CH₃CO)₂O, heat	13	268
Benzaldehyde	(CH₃CO)₂O, heat	73*	268
Acrylamide and			
Octanal	Concd. HCl, heat		505
Benzaldehyde	Concd. HCl, heat		505
Cinnamamide and			
Heptanal	No solvent, heat	—	517
Benzaldehyde	No solvent, heat	62	284, 518
3-Chlorosalicylaldehyde	No solvent, heat	72	528
3,5-Dichlorosalicylaldehyde	No solvent, heat	90	528
Piperonal	No solvent, heat	82	519
6-Nitropiperonal	No solvent, heat	83	520

Note: References 382 to 637 are on pp. 266–269.

* Excerpt when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—*Continued*

Symmetrical N,N'-Alkylidene-*bis* and N,N'-Arylidene-*bis* Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aliphatic Amides (contd.)			
α-Methylcinnamamide and Benzaldehyde	No solvent, heat	48	284
(CONH₂)₂ and Benzaldehyde	C₂H₅O₂CCONH₂, C₆H₅CHO, 150° Product:	—	285
(C₂H₅)₂C((CONH₂)₂ and Cinnamaldehyde Benzaldehyde	No solvent, acid, 150° No solvent, acid, 150° Products:	— —	286 286
(CH₂CONH(C₆H₅)₂ and Heptanol	No solvent, 110° (product not characterized)	—	270

Aromatic Amides

Benzamide and Acetaldehyde

Reactants and conditions	Yield		References
$(CH_3CO)_2O$, heat	48		281
H_2O, acid		63, 80	531
$n\text{-}C_3H_7OCH=CH_2$, $C_6H_5CONH_2$, heat			232, 233
CH_3CHO, C_6H_5CN, conced. H_2SO_4			245, 527
CH_3CHO, C_6H_5CN, HCl, H_2O, 300°			496
CH_3CHO, NH_4OH, C_6H_5COCl			532
Chloral			
$[C_6H_5CONHCH(CCl_3)]_2O$, 140°/40 mm.			95
CCl_3CHO, C_6H_5CN, heat	37		245, 261, 296
CCl_3CHO, C_6H_5CN, conced. H_2SO_4	67		290
Bromal			
CBr_3CHO, $C_6H_5CONH_2$, heat			245
β-Phenylpropionaldehyde			
No solvent, heat	40		275, 516
$CH_3CH(Cl)CHO$			
RCHO, C_6H_5CN, conced. H_2SO_4			246
Valeraldehyde			
$n\text{-}C_4H_9CHO$, C_6H_5CN, conced. H_2SO_4			245
Heptanal			
No solvent, heat			285, 517
Cyclohexanecarboxaldehyde			
$(CH_3CO)_2O$, heat	69		280
Cinnamaldehyde			
No solvent, heat	55		275
Benzaldehyde			
$(CH_3CO)_2O$, heat	43		281
$(CH_3CO)_2O$, heat	78		85
No solvent, heat	27		284
			518, 522, 523,
			533
o-Chlorobenzaldehyde			
No solvent, heat	Good		518
o-Nitrobenzaldehyde			
H_2O, acid	54		278
No solvent, heat			274
m-Nitrobenzaldehyde			
H_2O, acid			278
No solvent, heat	80		269

Note: References 382 to 537 are on pp. 266–289.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—*Continued*

SYMMETRICAL N,N'-ALKYLIDENE-*bis* AND N,N'-ARYLIDENE-*bis* DERIVATIVES OF AMIDES, LACTAMS,
IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Aromatic Amides (contd.)			
Benzamide (*contd.*) and			
p-Nitrobenzaldehyde	No solvent, heat	80	269
5-Chlorosalicylaldehyde	Pyridine	—	271
3,5-Dichlorosalicylaldehyde	No solvent, heat	—	271
o-Anisaldehyde	No solvent, heat	40–60	296*a*
m-Anisaldehyde	No solvent, heat	40–60	296*a*
p-Anisaldehyde	No solvent, heat	40–60	296*a*, 524
Piperonal	No solvent, heat	64	519
6-Bromopiperonal	No solvent, heat	4	525
6-Nitropiperonal	No solvent, heat	25	520
m-Tolualdehyde	Pyridine	37	273
p-Tolualdehyde	Pyridine or heat alone	50	276
1-Naphthaldehyde	$(CH_3CO)_2O$, heat	43	282
2-Naphthaldehyde	$(CH_3CO)_2O$, heat	59	282
9-Anthraldehyde	$(CH_3CO)_2O$, heat	38	282
1-Pyrenecarboxaldehyde	$(CH_3CO)_2O$, heat	75	282
2-Furaldehyde	No solvent, heat	40	284
2-Thiophenecarboxaldehyde	$(CH_3CO)_2O$, heat	68	280, 282
2-Pyrrolecarboxaldehyde	$(CH_3CO)_2O$, heat	0	280
Picolinaldehyde	No solvent, heat	99	280
Nicotinaldehyde	No solvent, heat	73	280
Isonicotinaldehyde	No solvent, heat	27	280
3-Indolecarboxaldehyde	$(CH_3CO)_2O$, heat	60	280
Benzanilide and			
Heptanal	No solvent, 110°	—	270

o-Chlorobenzamide and Acetaldehyde	CH$_3$CHO, ArCN, concd. HBr	—	497
	CH$_3$CHO, ArCN, HCl, H$_2$O, 289*	—	500
p-Chlorobenzamide and Chloral	CCl$_3$CHO, ArCN, 95% H$_2$SO$_4$	—	296
o-Nitrobenzamide and Benzaldehyde	(CH$_3$CO)$_2$O, HCl, heat	40	85
z-Nitrobenzamide and Heptanal	No solvent, heat	—	285
o-Anisamide and Benzaldehyde	H$_2$O, acid	—	365
o-Toluamide and o-Nitrobenzaldehyde	No solvent, heat	47?	274
2-CH$_3$-5-O$_2$NC$_6$H$_3$CONH$_2$ and Benzaldehyde	No solvent, heat	—	534
m-Nitrobenzaldehyde	No solvent, heat	—	534
p-Nitrobenzaldehyde	No solvent, heat	—	534
Piperonal	No solvent, heat	—	534
p-Toluamide and Chloral	CCl$_3$CHO, ArCN, 95% H$_2$SO$_4$	40	290
1-Naphthamide and Acetaldehyde	(CH$_3$CO)$_2$O, heat	58	268
Benzaldehyde	No solvent, heat	93	268
Nicotinamide and Acetaldehyde	No solvent, heat	9	268
Benzaldehyde	No solvent, heat	66	268

Note: References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amido and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued

Symmetrical N,N'-Alkylidene-bis and N,N'-Arylidene-bis Derivatives of Amides, Lactams, Imides, Carbamyl Compounds, and Sulfonamides

$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$

Derivative of	Method*	Yield, %	References
Lactams and Imides			
2-Pyrrolidinone and Acetaldehyde	H_2O, acid	Good	247
Phthalimide and Benzaldehyde	$(CH_3CO)_2O$, heat	0	85
Carbamyl Compounds			
Ethyl carbamate and Acetaldehyde	H_2O, acid	78	173, 250, 531
	H_2O, acid	—	173
Chloroacetaldehyde	C_2H_5OH, HCN, Cl_2	—	266, 267
	H_2O, acid	—	173
Dichloroacetaldehyde	C_2H_5OH, HCN, Cl_3	—	266, 267
Chloral	$NH_2CO_2C_2H_5$, $(C_2H_5O_2CNHCHClCCl_3)_2O$	38	94
	$NH_2CO_2C_2H_5$, Cl_3	20	94
	$NH_2CO_2C_2H_5$, CCl_3CHO, acid	—	94
	$[C_2H_5O_2CNHCH(CCl_3)]_2O$, PCl_5	—	95
Bromoacetaldehyde	$NH_2CO_2C_2H_5$, Br_2	—	230
Dibromoacetaldehyde	$NH_2CO_2C_2H_5$, Br_2	—	230
Bromal	H_2O, acid	—	173
	C_2H_5OH, HCN, Br_2	—	267
	$NH_2CO_2C_2H_5$, Br_2	27	535
	$NH_2CO_2C_2H_5$, CBr_3CHO, acid	—	535

Valeraldehyde	H₂O, acid	—	173
Cinnamaldehyde	H₂O, acid	—	277
Glyoxylic acid	Heat alone	—	230
Benzaldehyde	H₂O, acid	—	173
o-Nitrobenzaldehyde	NaO₂CH₃	—	230
m-Nitrobenzaldehyde	H₂O, acid	—	278
p-Anisaldehyde	H₂O, acid	—	278
Piperonal	H₂O, acid	—	277
2-Furaldehyde	H₂O, acid	98	529
n-Propyl carbamate and			277
Acetaldehyde	H₂O, acid	—	
Benzaldehyde	H₂O, acid	—	277
NH₂CS(OC₂H₅) and			277
Valeraldehyde			
Urea and†			
Chloral	H₂O, acid		277
H₂NCONHCHOHCCl₃, urea, (CH₃CO)₂O			473
	Heat alone		
CH₃CHClCCl₂CHO	Heat alone	Poor	536
Valeraldehyde	H₂O alone	—	536
Heptanal	C₂H₅OH alone	—	272
Acrolein	H₂O alone	—	272
Cinnamamide	H₂O alone	—	272
Benzaldehyde	H₂O alone	—	123, 272
s-Nitrobenzaldehyde	C₂H₅OH alone	—	272
Salicylaldehyde	C₂H₅OH alone	—	272
	C₂H₅OH alone	—	272

Note   References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amido and aldehyde are unnamed reactants in this column.

† The products are of the type H₂NCONHCH₂CHR.

TABLE XXXIV—Continued

SYMMETRICAL N,N'-ALKYLIDENE-bis AND N,N'-ARYLIDENE-bis DERIVATIVES OF AMIDES, LACTAMS,
IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

$$2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$$

Derivative of	Method*	Yield, %	References
Carbamyl Compounds (contd.)			
Urea (contd.) and†			
5-Chlorosalicylaldehyde	C_2H_5OH alone	—	271
3,5-Dichlorosalicylaldehyde	C_2H_5OH alone	—	271
p-Anisaldehyde	C_2H_5OH alone	—	272
o-Ethoxybenzaldehyde	C_2H_5OH alone	—	272
Cuminaldehyde	C_2H_5OH alone	—	123
Hydantoin and	Hydantoin, $CH_2(OC_2H_5)_2$, CH_3CO_2H, H_2SO_4, heat	96	290
Acetaldehyde			
Chloroacetaldehyde	Hydantoin, $CH_2ClCH(OC_2H_5)_2$, CH_3CO_2H, H_2SO_4, heat	70	290
Sulfonamides			
p-Toluenesulfonamide and	$ArSO_2NH_2$, $C_6H_5OCH=CH_2$, acid	11	232
Acetaldehyde			

Note: References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

† The products are of the type $(H_2NCONH)_2CHR$.

TABLE XXXV

Unsymmetrical N,N'-Arylidenebisamides[384]

$$RCONH_2 + R'CONH_2 + ArCHO \xrightarrow[\text{No solvent}]{\text{Heat}} RCONHCH(Ar)NHCOR'$$

R	R'	Ar	Yield, %
CH_3	C_6H_5	C_6H_5	30
CH_3	$C_6H_5CH=CH$	C_6H_5	39
CH_3	$C_6H_5CH=C(CH_3)$	C_6H_5	38
CH_3	C_6H_5	C_6H_5	42
CH_3	C_6H_5	2-Furyl	25
CH_3	$C_6H_5CH=CH$	2-Furyl	26
C_2H_5	$C_6H_5CH=CH$	C_6H_5	33
C_2H_5	$C_6H_5CH=C(CH_3)$	C_6H_5	30
C_2H_5	C_6H_5	C_6H_5	38
$C_6H_5CH=CH$	$C_6H_5CH=C(CH_3)$	C_6H_5	25
$C_6H_5CH=CH$	C_6H_5	C_6H_5	29
$C_6H_5CH=C(CH_3)$	C_6H_5	C_6H_5	26

Note: References 382 to 537 are on pp. 266–269.

TABLE XXXVI

Amidomethanesulfonic Acids and Salts

Sulfonic Acid Derivative	References (Yield, %)
$CH_3(CH_2)_7CH=CH(CH_2)_7CONHCH_2SO_3Na$	537
$C_6H_5CONHCH_2SO_3Na$	132
$p\text{-}CH_3OC_6H_4CONHCH_2SO_3Na$	132 (60)
$o\text{-}C_6H_4(CO)_2NCH_2SO_3H$	309 (13)
$C_6H_5SO_2NHCH_2SO_3Na$	132

$\overset{\displaystyle SO_2NHCH_2SO_3Na}{\underset{\displaystyle SO_2NHCH_2SO_3Na}{\bigcirc}}$ 132

Note: References 382 to 537 are on pp. 266–269.

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INTRODUCTION

In 1953 Wittig and Geissler[1] found that reaction of benzophenone with methylenetriphenylphosphorane gave 1,1-diphenylethylene and triphenylphosphine oxide in almost quantitative yield; the phosphorane had been prepared from triphenylmethylphosphonium bromide and phenyllithium. This discovery led in the following years to the development of

$$[(C_6H_5)_3\overset{+}{P}—CH_3]Br^\ominus + C_6H_5Li \rightarrow (C_6H_5)_3P=CH_2 + C_6H_6 + LiBr$$

$$(C_6H_5)_3P=CH_2 + (C_6H_5)_2C=O \rightarrow (C_6H_5)_2C=CH_2 + (C_6H_5)_3P=O$$
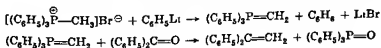
[1] Wittig and Geissler, Ann., 580, 44 (1953)

a new method for the synthesis of olefins[2-6] which, under the name Wittig reaction, soon attained importance in preparative organic chemistry.

One advantage of this new method is that the carbonyl group is replaced specifically by a carbon-carbon double bond without the formation of isomeric olefins. In contrast, the older method of converting carbonyl

$$
\begin{array}{c}
\text{R'CH}_2 \\
\diagdown \\
\text{C=O} + (\text{C}_6\text{H}_5)_3\text{P=CHR}''' \rightarrow \\
\diagup \\
\text{R''CH}_2
\end{array}
\qquad
\begin{array}{c}
\text{R'CH}_2 \\
\diagdown \\
\text{C=CHR}''' \\
\diagup \\
\text{R''CH}_2
\end{array}
$$
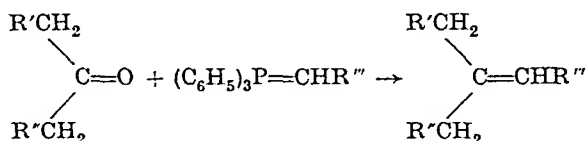
compounds to olefins using the Grignard reaction followed by dehydration of the resulting carbinol usually gives a mixture of isomeric olefins.

Another advantage of the Wittig reaction is that it is carried out in alkaline medium and usually under very mild conditions. Consequently it is the only method available for the preparation of sensitive olefins such as carotenoids, methylene steroids, and other natural products.

As early as 1919 Staudinger and Meyer[7,8] showed that the reaction of diphenylmethylenetriphenylphosphorane (1) with phenyl isocyanate gave N-phenyldiphenylketeneimine; but this discovery did not lead to the

$$(\text{C}_6\text{H}_5)_3\text{P=C}(\text{C}_6\text{H}_5)_2 + \text{C}_6\text{H}_5\text{N=C=O} \rightarrow \text{C}_6\text{H}_5\text{N=C=C}(\text{C}_6\text{H}_5)_2$$
$$\mathbf{1}$$
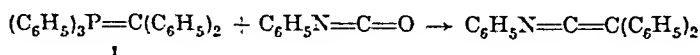
discovery of a new synthesis of olefins. One reason is the unusual stability of the phosphorane 1, which could not be made to react with normal carbonyl compounds. It has been found that, even with diphenylketene, reaction will occur only under forcing conditions (at 140° in benzene under pressure).[9-11]

$$(\text{C}_6\text{H}_5)_3\text{P=C}(\text{C}_6\text{H}_5)_2 + (\text{C}_6\text{H}_5)_2\text{C=C=O} \rightarrow (\text{C}_6\text{H}_5)_2\text{C=C=C}(\text{C}_6\text{H}_5)_2$$
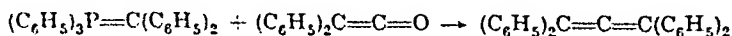
obtained from triphenylphosphine and diphenyldiazomethane. This

$$(C_6H_5)_3P + \overset{+}{N} = N = \overset{-}{C}(C_6H_5)_2 \rightarrow$$

$$(C_6H_5)_3P = N = N = C(C_6H_5)_2 \xrightarrow[190°]{-N_2} (C_6H_5)_3P = C(C_6H_5)_2$$

$$\qquad\qquad 2 \qquad\qquad\qquad\qquad\qquad 1$$
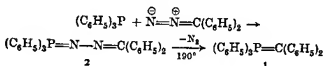
roundabout method could not be extended to the preparation of other phosphoranes since, in the pyrolysis of phosphazines, ketazines are usually formed instead.[7] It was not until the development of modern techniques in organometallic chemistry that reactive methylene phosphoranes became easily accessible and led to routes to olefins in good yields from a variety of aldehydes and ketones

This chapter includes the more important literature to the end of 1962 and a few selected articles published in 1963. Other reviews have been published elsewhere.[12-17a]

ALKYLIDENE TRIPHENYLPHOSPHORANES

Structure and Properties of Ylides

The existence of pentaphenylphosphorane[18] shows that, unlike nitrogen, phosphorus is capable of being pentacovalent, since it can expand its valency shell to 10 electrons by inclusion of d orbitals. Alkylidene phosphoranes can therefore be considered as resonance hybrids of two limiting structures, the ylide form 3a and the ylene form 3b. An in-

$$(R)_3\overset{+}{P} - \overset{-}{C} \overset{R_1}{\underset{R_2}{}} \longleftrightarrow (R)_3P = C \overset{R_1}{\underset{R_2}{}}$$

$$\qquad 3a \qquad\qquad\qquad 3b$$
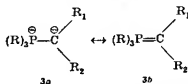
dication that alkylidene phosphoranes possess some ylene character was obtained from a kinetic study which showed that tetramethylphosphonium iodide is converted to the ylide much faster than is tetramethylammonium iodide, despite the fact that the protons in the phosphonium salt are under the influence of weaker repulsive Coulomb forces than those

[11] Levisalles, Bull. Soc. Chim. France, 1958, 1021.
[12] Schöllkopf, Angew. Chem., 71, 260 (1959).
[13] Pelc, Chem. Listy, 53, 177 (1959) [C.A., 53, 7965a (1959)].
[14] Kostka, Wiadomości Chem., 12, 521 (1958).
[15] Trippett, Advan. Org. Chem., 1, 83 (1960).
[16] Yanovskaya, Usp. Khim., 30, 813 (1961) [C.A., 56, 1323a (1962)].
[17a] Trippett, Quart. Rev., 17, 406 (1963).
[18] Wittig and Rieber, Ann., 562, 187 (1949).

in the ammonium salt (bond distances: P—C, 1.87 Å; N—C, 1.47 Å).[19] This greater tendency for the formation of phosphorus ylides reflects stabilization of the transition state by p-d orbital overlap.

The reactivity of alkylidene phosphoranes is determined by the distribution of the negative charge in the molecule, which in turn depends on the nature of the substituents R_1 and R_2 in the alkylidene portion as well as of the groups R on phosphorus. Thus the nucleophilic character of the phosphorane is decreased and the stability of the phosphorane increased if the lone electron pair on the α-carbon atom of form 3a is delocalized into groups R_1 and R_2. Generally speaking, electron-withdrawing substituents R_1 and R_2 will stabilize the negative charge and consequently reduce the reactivity of the ylide. Methylenetriphenyl-phosphorane (3a, 3b, $R_1 = R_2 = H$), where there is no such interaction, is an extremely reactive and unstable phosphorane of high nucleophilicity.

The groups R on phosphorus also influence the reactivity of the alkylidene phosphoranes since they may be capable of increasing or decreasing the d-orbital resonance with a consequent change in the relative importance of form 3b in the resonance hybrid. Decreased d-orbital resonance would result in greater importance of the ylide form 3a and therefore increased reactivity of the phosphorane. Investigations of the ultraviolet spectra of polyphenyl derivatives of phosphorus led to the conclusion that the formation of double bonds with inclusion of d orbitals is possible only if the central atom is positively charged in the single-bonded structure.[20–22] Applied to the alkylidene phosphoranes, this would mean that the ylene form 3b would be the more important the larger the formal charge on phosphorus. Electron-withdrawing groups R on phosphorus will, other things being equal, increase the d-orbital resonance and therefore favor the ylene form 3b, whereas electron-releasing groups will increase the importance of the ylide form 3a. These hypotheses are supported by investigations of transition metal complexes in which trivalent phosphorus occurs as a ligand and forms π as well as σ bonds with the metal. It has been shown that the capability for the formation of π bonds decreases in the series: $PF_3 > PCl_3 > P(OCH_3)_3 > P(C_3H_7\text{-}n)_3$. i.e., in the same sequence as the positive inductive effect ($+I$ effect) of substituents on phosphorus.[23]

Subsequently, studies were made of the ultraviolet and visible spectra of a series of planar complexes of the structure *trans*-[L. piperidine PtCl$_2$], where the ligand L was an aliphatic amine. phosphine. etc. Again

the extent of the phosphorus d-orbital participation in the interaction with the metal increases with increasing $+I$ effect of the groups on phosphorus: $L = P(C_3H_7 \cdot n)_3 < L = P(OCH_3)_3$.[24] Finally, studies of the carbonyl stretching frequency in the infrared spectra of nickel dicarbonyl-diphosphines $[Ni(CO)_2(PR_3)_2]$[25] and of complexes of the structure $(PR_3)_3Cr(CO)_3$[26] showed that the d-orbital participation in the metal phosphorus bond decreases in the series $PCl_3 > P(OC_6H_5)_3 > P(OC_2H_5)_3 > P(C_6H_5)_3 > P(C_4H_9 \cdot n)_3$, i.e., again following the $+I$ effect. Similar results using ^{31}P nuclear magnetic resonance spectroscopy were obtained.[27]

It would therefore be expected that alkylidene trialkylphosphoranes, in which the formal positive charge on phosphorus is reduced by the inductive effect of the alkyl groups, would under otherwise equal conditions be more reactive than alkylidene triphenylphosphoranes in which the $+I$ effect of the phenyl groups has the opposite effect. This is the case. Carbomethoxymethylenetricyclohexylphosphorane (4), for instance, is a stronger base than carbomethoxymethylenetriphenylphosphorane (5), and, unlike the latter, is sensitive to water.[28] The same explanation
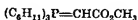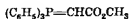
$$(C_6H_{11})_3P = CHCO_2CH_3 \qquad\qquad (C_6H_5)_3P = CHCO_2CH_3$$
$$\qquad\qquad 4 \qquad\qquad\qquad\qquad\qquad\qquad 5$$

rationalizes the increased stability of fluorenylidenetriphenylphosphorane as compared to that of fluorenylidene trialkylphosphoranes.[29] In general, the conjugate acid of a phosphorane should be the stronger the more important the ylene form 3b (and consequently the more important the d-orbital resonance); i.e., a more acidic phosphonium salt will be related to a less reactive phosphorane, and vice versa. It is possible to estimate the reactivity of an ylide from the pK_a value of its conjugate acid.[29]

The discussion of the mechanism of the Wittig reaction will show, however, that alkylidene trialkylphosphoranes are superior to alkylidene triphenylphosphoranes only in certain special cases.

The Wittig reagents may be divided into two groups according to their reactivity. The first and larger group includes the alkylidene phosphoranes of low stability and high reactivity, whereas the second group comprises the highly stable unreactive resonance-stabilized alkylidene phosphoranes.

[24] Chatt, Gamlen, and Orgel, *J. Chem. Soc.*, 1959, 1047.
[25] Meriwether and Fiene, *J. Am. Chem. Soc.*, 81, 4200 (1959).
[26] Abel, Bennett, and Wilkinson, *J. Chem. Soc.*, 1959, 2323.
[27] Meriwether and Leto, *J. Am. Chem. Soc.*, 83, 3192 (1961).
[28] Bestmann and Kratzer, *Chem. Ber.*, 95, 1894 (1962).
[29] Johnson and LaCount, *Tetrahedron*, 9, 130 (1960).

Phosphoranes containing substituents in the alkylidene group that have little effect on the carbanion character of the molecule are found in the first group. These Wittig reagents are markedly nucleophilic and react readily at low temperatures with carbonyl and other polar groups.

The second group consists of phosphoranes with electron-withdrawing substituents in the alkylidene portion which decrease the nucleophilicity to a certain extent and, in some cases, completely prevent the attack on a carbonyl group. Unlike the phosphoranes of the first group, they are essentially stable toward hydrolysis. For instance, the acylmethylene triphenylphosphoranes[30,31] are colorless crystalline compounds that are hydrolyzed only at elevated temperatures. This stability is probably due to resonance between the limiting structures 6a to 6c in which the carbonyl group is included. This is reflected in the shift of the carbonyl band in the infrared spectrum to 6.5–6.7 μ.[32] In spite of this resonance stabili-

$$(C_6H_5)_3\overset{\ominus}{P}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-R \leftrightarrow (C_6H_5)_3P=CH-\overset{O}{\overset{\|}{C}}-R \leftrightarrow (C_6H_5)_3\overset{\ominus}{P}-CH=\overset{O\ominus}{\overset{|}{C}}-R$$

$$\quad\quad\quad 6a \quad\quad\quad\quad\quad\quad\quad\quad\quad 6b \quad\quad\quad\quad\quad\quad\quad\quad 6c$$
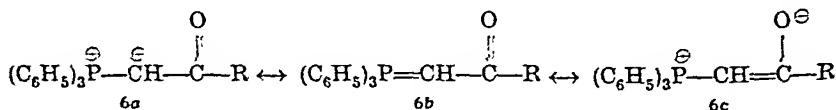
zation the acylmethylene triphenylphosphoranes undergo the Wittig reaction with reactive carbonyl compounds such as benzaldehyde, but not with cyclohexanone under the same conditions.[31] Similarly formyl-methylenetriphenylphosphorane (6, R = H), a stable compound of melting point 187°, reacts readily with aldehydes in boiling benzene but not with ketones.[33]

In the synthesis of olefins having electron-withdrawing groups on the α-carbon atom the reagent of choice is often the anion derived from a phosphonate ester. For example,

$$(C_2H_5O)_2\overset{}{\underset{\overset{|}{O}}{P}}-\overset{\ominus}{C}HCO_2C_2H_5$$
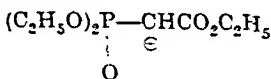
will react readily with cyclohexanone to form ethyl cyclohexylidene-acetate. Reagents of this type are discussed on pp. 379–382.

The preparatively important carbalkoxymethylene triphenylphos-phoranes 7a will also react with ketones but only under forcing con-ditions.[34-37] However, the phosphorane 7a reacts readily with cyclic

and methyl ketones in the presence of benzoic acid as a catalyst.[38] Reaction with aldehydes, on the other hand, occurs readily.[3,39]

$$(C_6H_5)_3P=CHCO_2R \qquad (C_6H_5)_3P=CHCONH_2 \qquad (C_6H_5)_3P=CHCN$$

<div align="center">7a   7b   7c</div>
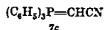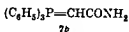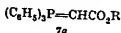
Carbalkoxymethylene triphenylphosphoranes (7a) are stable crystalline compounds which can be kept for a long time without decomposition. Participation of the ester group in charge delocalization is evident from the shift of the carbonyl band in the infrared to 6.15 μ,[40] as well as from the stability of the compounds. Carbamidomethylenetriphenylphosphorane (7b)[41] and cyanomethylenetriphenylphosphorane (7c)[41–43] also belong to this group of stable phosphoranes.

Replacement of the second hydrogen atom in the methylene group by an electron-delocalizing substituent results in further decrease of the reactivity of the phosphoranes to such an extent that they may become unreactive even toward aldehydes. Examples of such phosphoranes are diphenylmethylenetriphenylphosphorane (1),[8] 4-nitrobenzhydrylenetriphenylphosphorane (8),[44] and compounds of type 9,[45] whose ultraviolet spectra show that the negative charge is extensively delocalized into the two groups X and Y.

$$(C_6H_5)_3P=C(C_6H_5)_2 \qquad (C_6H_5)_3P=C{\overset{C_6H_4NO_2\text{-}p}{\underset{C_6H_5}{}}} \qquad (C_6H_5)_3P\overset{\ominus}{-}C{\overset{X}{\underset{Y}{}}}$$

<div align="center">1   8   9</div>

<div align="center">(X, Y = CO$_2$R, CN, SO$_2$C$_6$H$_5$, COCH$_3$)</div>
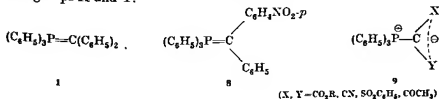
The methylene carbon atom may also be made part of a quasi-aromatic system with a resulting decrease in the carbanion character of the ylide. Cyclopentadienylidenetriphenylphosphorane (10),[46,47] for instance, is a yellow crystalline compound, m.p 229–231°, stable to prolonged heating with concentrated aqueous or ethanolic potassium hydroxide It does not react with benzophenone, fluorenone, or cyclohexanone on heating in

[38] Ruchardt, Eichler, and Panse, *Angew. Chem.*, **75**, 858 (1963).
[39] Isler, Gutmann, Montavon, Rüegg, and Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).
[40] Bestmann and Schulz, *Chem. Ber.*, **95**, 2921 (1962)
[41] Trippett and Walker, *J. Chem. Soc.*, 1959, 3874.
[42] Novikov and Shvekhgeimer, *Izv. Akad. Nauk SSSR, Otd. Khim Nauk*, 1959, 2061 [*C.A.*, **55**, 13353g (1961)].
[43] Schiemenz and Engelhard, *Chem Ber.*, **94**, 578 (1961).
[44] Drefahl, Plotner, and Scholz, *Z. Chem.*, **1**, 93 (1961).
[45] Horner and Oediger, *Chem Ber.*, **91**, 437 (1958).
[46] Ramires and Levy, *J. Org. Chem.*, **21**, 488 (1956).
[47] Ramires and Levy, *J. Am. Chem. Soc.*, **79**, 67 (1957).

diethyl ether, chloroform, ethanol, or tetrahydrofuran for 120 hours. Reaction with benzaldehyde appears to occur, but no pure products could be isolated.
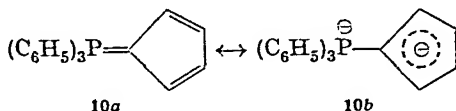
Fluorenylidenetriphenylphosphorane (11)[48,49] is considerably more reactive; it is hydrolyzed by ethanolic sodium hydroxide, and it undergoes the Wittig reaction with a number of aldehydes to give olefins. The dipole moment of 7.09 D points to the importance of resonance form 11b in the hybrid. Replacement of the phenyl groups on phosphorus by
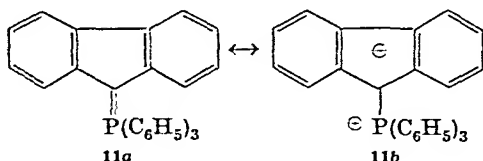
alkyl groups in 11[29,50] results in a marked increase in reactivity. Thus the hydrolysis of fluorenylidenetrimethylphosphorane[50,51] occurs readily under the influence of atmospheric moisture, and fluorenylidenetributylphosphorane[29] may even be made to react with a number of ketones.

Preparation of Alkylidene Phosphoranes

The Wittig reagents are usually prepared by the action of bases on the easily accessible triphenylalkylphosphonium halides. Formation of
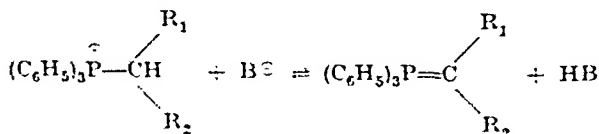
alkylidene phosphoranes by removal of a proton from the salt under the influence of base is a reversible reaction. The choice of conditions depends entirely on the nature of the desired ylide. The air- and moisture-sensitive phosphoranes of the first group have to be prepared in an anhydrous medium under an atmosphere of inert gas, employing

organometallic compounds as proton acceptors. In one method[2] an ether solution of phenyllithium or butyllithium is added under nitrogen to a suspension of 1 equivalent of the phosphonium salt in ether, tetrahydrofuran, or other suitable solvent. The reaction usually occurs in the cold, and formation of the alkylidene phosphoranes can be followed by the appearance of an intense yellow or red coloration.

A variation of this method consists in preparing the ylide in liquid ammonia with sodium amide as the base and then replacing ammonia by diethyl ether or tetrahydrofuran.[52] Sodium amide has also been used in other solvents, such as benzene, diethyl ether, or tetrahydrofuran.[53]

Alkylidene phosphoranes that do not react with a carboxamide function can also be prepared in dimethylformamide as the solvent; in these reactions, sodium acetylide has proved to be particularly useful as a base.[54,55] Since many phosphonium salts can be readily prepared in dimethylformamide, the Wittig reaction can be carried out without isolation of the quaternary salt.

Another method for the preparation of alkylidene phosphoranes employs alkali metal alkoxides as proton acceptors, usually in the corresponding alcohol as solvent.[3] The simplicity of this method is gaining more and more attention for it. The alkoxide procedure permits preparation of unstable ylides directly in the presence of carbonyl compounds, thus minimizing side reactions.

Since, unlike the reactive phosphoranes of the first group, the resonance-stabilized ylides of the second group are stable toward hydrolysis, they can be prepared by the action of alkali metal hydroxides on an aqueous solution of the phosphonium salt.[32,56] The phosphorane usually precipitates in crystalline form and can be dried in air. With sufficiently acidic phosphonium salts, weaker bases can also be used. For instance, fluorenylidenetriphenylphosphorane (11)[13] has been prepared by the action of ammonium hydroxide on the corresponding phosphonium salt, and p-nitrobenzylidenetriphenylphosphorane (12)[57] has been prepared

$$(C_6H_5)_3P=CHC_6H_4NO_2\text{-}p$$

P(C₆H₅)₃

11   12
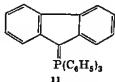
[52] Wittig, Eggers, and Duffner, *Ann.*, **619**, 10 (1958).

[53] Wittig and Pommer, Ger. pat. 1,003,730 (to BASF) [*C A.*, **53**, 16063c (1959)]

[54] Wittig and Pommer, Ger. pat. 954,247 (to BASF) [*C A.*, **53**, 227e (1959)].

[55] Pommer, Wittig, and Sarneck, Ger pat. 1,026,745 (to BASF) [*C.A.*, **54**, 11074f (1960)]

[56] Gerecke, Rysen, and Zeller, Ger. pat. 1,125,922 (to Hoffman-La Roche), 1938, corresponds to U.S. pat. 2,912,467 [*C.A.*, **54**, 225ie (1960)].

[57] Kröhnke, *Chem. Ber.*, **83**, 291 (1950).

using sodium carbonate as the base. Carbomethoxymethyltriphenylphosphonium bromide also reacts with sodium carbonate, whereas sodium hydroxide must be used in order to convert the less acidic carbomethoxymethyltricyclohexylphosphonium bromide to its ylide.[28] Triethylamine[53-60] and pyridine[58,60] have also been used for the preparation of resonance-stabilized alkylidene phosphoranes.

Other methods for the preparation of alkylidene phosphoranes from phosphonium salts are known. Hydrogen bromide can be eliminated from triphenylbenzylphosphonium bromide with metallic sodium.[61]

$$[(C_6H_5)_3\overset{\oplus}{P}-CH_2C_6H_5]Br^\ominus + Na \rightarrow (C_6H_5)_3P{=}CHC_6H_5 + [H]$$
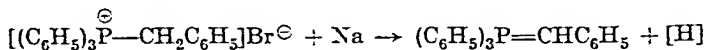
Ethylidenetriphenylphosphorane is obtained in very good yield by the action of methylsulfinyl carbanion on triphenylethylphosphonium bromide in dimethyl sulfoxide.[62,63] Finally it should be mentioned that

$$CH_3-\overset{\overset{\displaystyle O}{\diagup}}{\underset{\diagdown}{S}}\underset{CH_2}{\overset{\ominus}{\vdots}} \cdot Na^\ominus + (C_6H_5)_3\overset{\oplus}{P}C_2H_5Br^\ominus \rightarrow (C_6H_5)_3P{=}CHCH_3$$
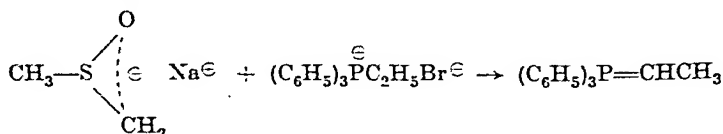
Coffmann and Marvel[64] were the first to prepare ylides by the organometallic route by allowing trityl sodium to react with triphenylalkylphosphonium salts.

The mechanism of ylide formation by the interaction of organolithium compounds with phosphonium salts was the subject of an interesting study.[65] The organic base not only removes a proton from the α-carbon atom (path A) but also adds to a certain extent to phosphorus, forming a presumably pentavalent intermediate which then collapses into alkylidenephosphorane and a hydrocarbon (path B). The formation of benzene.

$$(C_6H_5)_3\overset{\oplus}{P}-CH_3Br^\ominus \xrightarrow[\text{CH}_3\text{Li}]{A} (C_6H_5)_3P{=}CH_2 + CH_4$$

$$B\Big\downarrow CH_3Li$$

$$\underset{\underset{CH_3}{|}}{(C_6H_5)_3P-CH_3} \longrightarrow \underset{\underset{CH_3}{|}}{(C_6H_5)_2P{=}CH_2} + C_6H_6$$
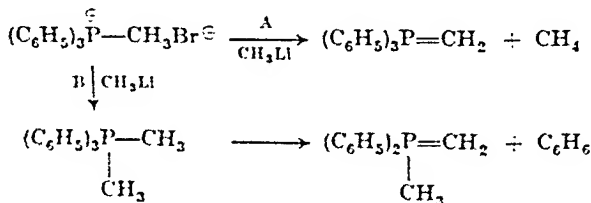
obtained in 20% yield, could take place only by path B. Similarly, interaction of triphenylmethylphosphonium bromide with p-deuterio-phenyllithium gave benzene in addition to deuteriobenzene.

$$(C_6H_5)_3\overset{\oplus}{P}-CH_3Br^{\ominus} + LiC_6H_4D \xrightarrow{A} (C_6H_5)_3P=CH_2 + C_6H_5D$$

$$\downarrow B$$

$$\begin{array}{c} (C_6H_5)_3P-CH_3 \\ | \\ C_6H_4D \end{array} \longrightarrow \begin{array}{c} (C_6H_5)_2P=CH_2 + C_6H_6 \\ | \\ C_6H_4D \end{array}$$
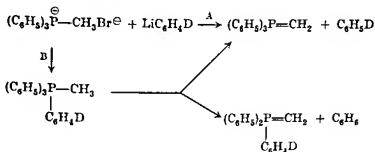
The reaction of tetraphenylphosphonium bromide with methyllithium must have proceeded via path B exclusively, since benzene was obtained in quantitative yield. Path A is ruled out in this reaction since the α-carbon atom does not carry a hydrogen atom.

$$(C_6H_5)_4\overset{\oplus}{P}Br^{\ominus} + CH_3L_1 \xrightarrow{B} (C_6H_5)_3P=CH_2 + C_6H_6$$
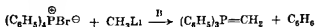
These results indicate that phenyllithium rather than butyllithium will be preferred for the organometallic preparation of ylides, since butyllithium may give rise to the formation of butylidene phosphoranes in addition to the desired ylide. It must be stressed, however, that

$$(C_6H_5)_3\overset{\oplus}{P}-\underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{CH}} Br^{\ominus} + C_4H_9L_1 \xrightarrow{A} (C_6H_5)_3P=\underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{C}} + C_4H_{10}$$

$$\downarrow B$$

$$\begin{array}{c} (C_6H_5)_3P-\overset{\overset{R_1}{|}}{\underset{\underset{R_2}{|}}{CH}} \\ | \\ C_4H_9 \end{array} \longrightarrow \begin{array}{c} (C_6H_5)_2P=\underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{C}} \\ | \\ C_4H_9 \end{array}$$

$$\begin{array}{c} (C_6H_5)_3P=\underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{CH}} \\ || \\ CHC_3H_7 \end{array}$$
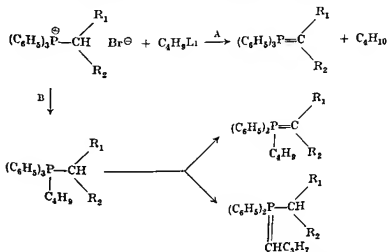
certain reactions proceed by path A exclusively. Thus the reaction of benzyltriphenylphosphonium bromide with methyllithium apparently

does not go by way of a pentavalent intermediate, since benzene was not a product.[65]

A side reaction involving attack of the base directly on phosphorus can also occur in the alkoxide method, but only at elevated temperatures.[66,67]

$$(C_6H_5)_3\overset{\ominus}{P}{-}CH_2C_6H_5\ Cl^{\ominus}\ +\ C_2H_5O^{\ominus}\ \rightarrow$$

$$(C_6H_5)_3PO\ +\ C_6H_5C_3H_7$$

The main reaction is the reversible removal of a proton from the α-carbon atom. The phosphorane so obtained is in equilibrium with the alcohol, as shown by the formation of tritium-labeled ylides on addition of C_2H_5OT.[68] The same method was used to prove the existence of a

$$(C_6H_5)_3P{=}CHR \quad \underset{-C_2H_5OT}{\overset{+C_2H_5OT}{\rightleftharpoons}}$$

$$(C_6H_5)_3\overset{\ominus}{P}{-}\underset{\underset{T}{|}}{C}HR \quad C_2H_5O^{\ominus} \quad \underset{+C_2H_5OH}{\overset{-C_2H_5OH}{\rightleftharpoons}} \quad (C_6H_5)_3P{=}CTR$$

resonance interaction in the allylidene phosphoranes in which the tritium label was found on both the α- and the γ-carbon atoms.

$$R_3P{=}CHCH{=}CHC_6H_5 \leftrightarrow R_3\overset{\oplus}{P}{-}\overset{\ominus}{C}HCH{=}CHC_6H_5 \leftrightarrow R_3\overset{\oplus}{P}{-}CH{=}CH\overset{\ominus}{C}HC_6H_5$$

$$\downarrow \begin{matrix} +C_2H_4OT \\ -C_2H_4OH \end{matrix}$$

$$R_3P{=}\underset{\underset{T}{|}}{C}{-}CH{=}CHC_6H_5 \ +\ R_3P{=}CH{-}CH{=}\underset{\underset{T}{|}}{C}C_6H_5$$

As far as is known, these ylides react in the Wittig reaction exclusively on the α-carbon atom, but the resonance effect is evident in some cases

by the *cis-trans* isomerization of the partial allylic double bond which occurs more or less readily at room temperature. Thus the ylene 13 reacts with cyclohexanone at −25° with the almost exclusive formation of the expected *cis*-diene 14, whereas at +40° a 20% yield of the *trans* isomer 15 is also obtained.[69] In order to get pure isomers, it is therefore

13

−25°   40°

14

15   + 14
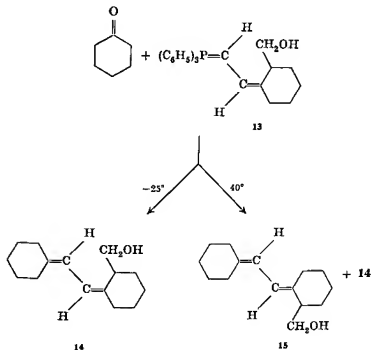
necessary to work at low temperatures. This requirement poses no problem in view of the high reactivity of the allylidene phosphoranes

Hydroxyl groups in the ylide may be protected by conversion to acetals or tetrahydropyranyl ethers [70–72] Example 13 shows that this is not absolutely necessary provided sufficient base is present to convert the alcohol to alkoxide.

Side reactions in the preparation of alkylidene phosphoranes from phosphonium salts are very rare and can usually be avoided by suitable choice of conditions. In fact, complications are to be expected only if the ylide carries a substituent in the β-position to the phosphorus atom which

[69] Harrison and Lythgoe, *J. Chem Soc.*, 1958, 843.

[70] Inhoffen, Bruckner, and Hess, *Chem. Ber.*, **93**, 1850 (1955).

[71] Bohlmann, Bornowski, and Herbst, *Chem. Ber.*, **93**, 1931 (1960).

[72] Bohlmann and Ruhnke, *Chem. Ber.*, **93**, 1945 (1960).

is prone to nucleophilic displacement, or if a proton in the β-position is so acidic that Hofmann elimination will be favored over ylide formation. Thus the ylides 16 and 17[73] decompose very readily, as evidenced by the rapid disappearance of the color.
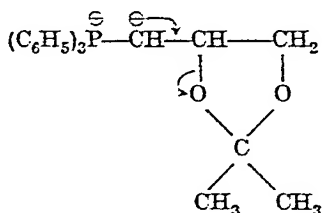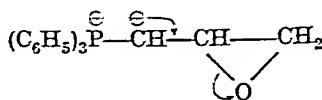
Halogen atoms also may undergo an intramolecular nucleophilic displacement, which in special cases leads to cyclic products.[74,75]
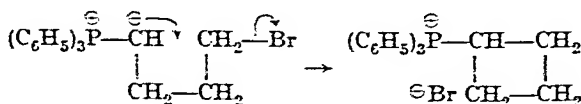
Attempts to prepare a heterocyclic phosphorus ylene from the phosphonium salt 18 were not successful; Hofmann elimination with ring opening occurred instead.[76] On the other hand, certain other cyclic
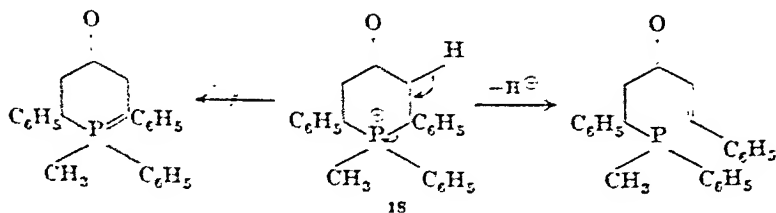
alkylidene phosphoranes can be prepared.[77]

The bis-phosphonium salt 19 also undergoes Hofmann elimination under the influence of phenyllithium in ether with the formation of triphenyl-vinylphosphonium bromide and triphenylphosphine, the mono ylide 20

being a probable intermediate.[52]

$$(C_6H_5)_3\overset{\oplus}{P}\text{---}CH_2CH_2\text{---}\overset{\oplus}{P}(C_6H_5)_3 \xrightarrow{C_6H_5Li}$$
$$\underset{Br^{\ominus}}{}\underset{Br^{\ominus}}{}$$
$$\mathbf{19}$$

$$(C_6H_5)_3\overset{\oplus}{P}\text{---}\overset{\ominus}{C}H\text{---}CH_2\text{---}\overset{\oplus}{P}(C_6H_5)_3 \longrightarrow (C_6H_5)_3\overset{\oplus}{P}\text{---}CH=CH_2 + (C_6H_5)_3P$$
$$\underset{Br^{\ominus}}{}\underset{Br^{\ominus}}{}$$
$$\mathbf{20}$$
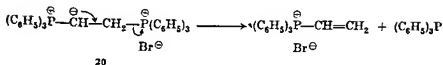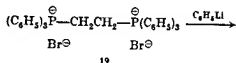
The ylide **22**, a vinylog of **20**, also eliminates triphenylphosphine by a process involving the electrons of the central double bond.[78,79]

$$(C_6H_5)_3\overset{\oplus}{P}\text{---}CH_2\text{---}CH=CH\text{---}CH_2\text{---}\overset{\oplus}{P}(C_6H_5)_3$$
$$\underset{Br^{\ominus}}{}\underset{Br^{\ominus}}{}$$
$$\mathbf{21}$$

$$\downarrow \scriptstyle{\begin{array}{c}C_6H_5Li\\ \text{or}\\ Na_2CO_3\end{array}}$$

$$(C_6H_5)_3\overset{\oplus}{P}\text{---}\overset{\ominus}{C}H\text{---}CH=CH\text{---}CH_2\text{---}\overset{\oplus}{P}(C_6H_5)_3$$
$$\underset{Br^{\ominus}}{}$$
$$\mathbf{22}$$

$$\downarrow$$

$$(C_6H_5)_3\overset{\oplus}{P}\text{---}CH=CH\text{---}CH=CH_2 + (C_6H_5)_3P$$
$$\underset{Br^{\ominus}}{}$$
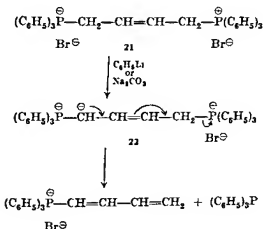
If such unstable alkylidene phosphoranes are encountered in the course of a Wittig reaction, it is necessary to carry out the condensation with carbonyl compounds very rapidly and, if possible, *in statu nascendi*. Best suited for this purpose is the alkoxide method which permits the addition of aldehydes or ketones before the ylide is prepared. Thus, if the bis-phosphonium salt **21** is treated with lithium ethoxide in ethanol in the presence of aldehydes,[79a] decomposition of the mono ylide **22** is prevented and the normal products of the Wittig reaction are obtained.

[78] H. Burger, Doctoral Dissertation, Universität Tübingen, 1958.

[79] Ford and Wilson, *J. Org. Chem.*, **26**, 1433 (1961).

[79a] Heitman, Sperna Weiland, and Huisman, *Koninkl. Ned. Akad. Wetenschap, Proc., Ser. B*, **64**, 165 (1961) [*C.A.*, **55**, 17562f (1961)].

Bifunctional ylides with several central double bonds or with a central triple bond (23, 24) can be prepared without complication by the organo-metallic method, since the initially formed mono ylides are more stable than the mono ylide 22.[80]

$(C_6H_5)_3P$ ⟍⟍ ⟋⟍ ⟋⟍ ⟋ $P(C_6H_5)_3$

23

$(C_6H_5)_3P$ ⟍⟍ ⟋ —C≡C— ⟍ ⟋ $P(C_6H_5)_3$

24
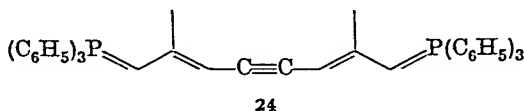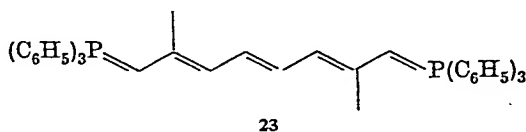
The interaction of bases with methylene bis(triphenylphosphonium bromide) (25)[81] leads to interesting ylides in which the two positively charged phosphorus atoms are separated by only one carbon atom. On addition of aqueous sodium carbonate there is first obtained the colorless, resonance-stabilized mono ylide 26, which is then converted under the influence of metallic potassium in diglycol dimethyl ether to the stable yellow hexaphenylcarbodiphosphorane 27.

$$(C_6H_5)_3\overset{\oplus}{P}-CH_2-\overset{\oplus}{P}(C_6H_5)_3$$

25

$$\Big\downarrow \text{Na}_2\text{CO}_3$$

$$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-\overset{\oplus}{P}(C_6H_5)_3 \leftrightarrow (C_6H_5)_3P=CH-\overset{\ominus}{P}(C_6H_5)_3 \leftrightarrow$$

26

$$(C_6H_5)_3\overset{\oplus}{P}-CH=P(C_6H_5)_3$$

$$\Big\downarrow \text{K}$$

$$(C_6H_5)_3P=C=P(C_6H_5)_3$$

$$\updownarrow$$

$$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}-\overset{\oplus}{P}(C_6H_5)_3, \quad \text{etc.}$$

27
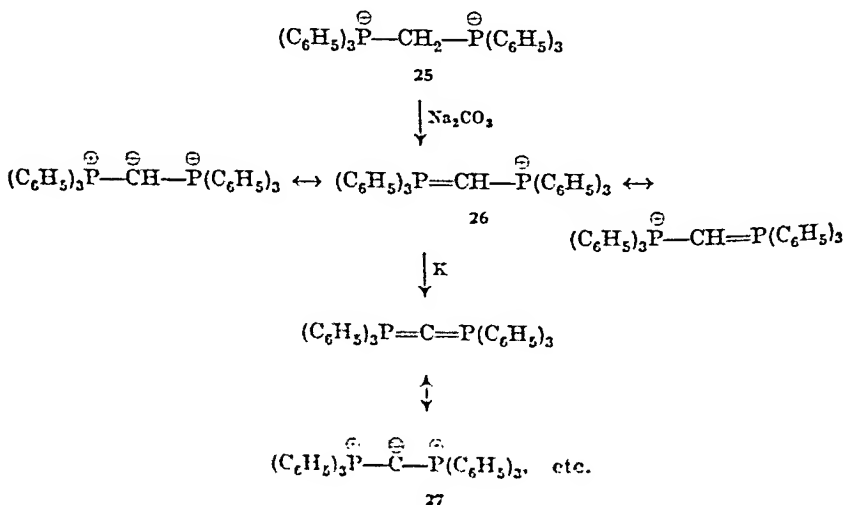
The same mono ylide **26** was obtained by the elimination of bromine from dibromomethyltriphenylphosphonium bromide with triphenylphosphine.[82]

$$(C_6H_5)_3\overset{\oplus}{P}-CHBr_2 + (C_6H_5)_3P \rightleftharpoons (C_6H_5)_3P=CHBr + (C_6H_5)_3PBr_2$$
$$Br^{\ominus}$$

$$\downarrow{\scriptstyle(C_6H_5)_3P}$$

$$(C_6H_5)_3P=CH-\overset{\oplus}{P}(C_6H_5)_3$$
$$Br^{\ominus}$$
$$\mathbf{26}$$
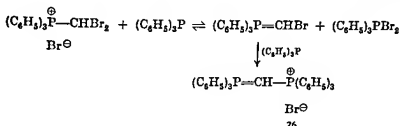
In the preparation of alkylidene phosphoranes from α-haloalkyl-phosphonium salts and organometallic compounds the possibility of halogen-metal interchange reactions must also be taken into account.[83,84]

$$(C_6H_5)_3P=CH_2 + C_6H_5Br$$

$$(C_6H_5)_3\overset{\oplus}{P}-CH_2Br \overset{C_6H_5Li}{\nearrow}$$
$$Br^{\ominus} \qquad \searrow$$

$$(C_6H_5)_3P=CHBr + C_6H_6$$
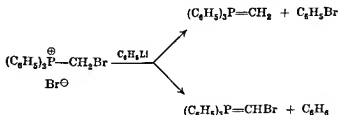
Bromomethyltriphenylphosphonium bromide will react with butyllithium in ether with the exclusive formation of methylenetriphenylphosphorane, whereas with lithium piperidide no halogen-metal interchange takes place.[84]

$$(C_6H_5)_3P=CHBr \xleftarrow{C_5H_{10}NLi} (C_6H_5)_3\overset{\oplus}{P}-CH_2Br \xrightarrow{C_4H_9Li} (C_6H_5)_3P=CH_2$$
$$Br^{\ominus}$$
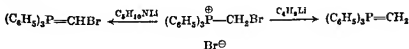
The interaction of bases with chloromethyltriphenylphosphonium halides leads to the formation of chloromethylenetriphenylphosphorane (**28**). Under the further influence of bases this compound undergoes an interesting rearrangement in which a chloride ion is lost and a phenyl group migrates from phosphorus to the methylene carbon atom [85,86]

[82] Ramirez, Desai, and McKelvie, *J. Am. Chem. Soc.*, **84**, 1745 (1962).
[83] Seyferth, Heeren, and Grim, *J. Org. Chem.*, **26**, 4783 (1961).
[84] Köbrich, *Angew. Chem.*, **74**, 33 (1962).
[85] Schlosser, *Angew. Chem.*, **74**, 291 (1962).
[86] Hellmann and Bader, *Tetrahedron Letters*, **1961**, 724.

Although the mechanism is not entirely clear, it may be formulated as in the accompanying equations.[85]

$$(C_6H_5)_3P{=}CHCl \ + \ R^{\ominus} \ \rightarrow \ (C_6H_5)_3\overset{\oplus}{P}{-}\overset{\ominus}{C}HCl$$
$$\hspace{7cm} \underset{R}{|}$$

28

$$\downarrow -Cl^{\ominus}$$

$$\underset{\underset{(C_6H_5)_2P{-}CH_2C_6H_5}{}}{\overset{O}{\overset{\|}{}}} \quad \xleftarrow{\text{When R} = \text{OH}} \quad (C_6H_5)_2P{=}CHC_6H_5$$
$$\hspace{10cm} \underset{R}{|}$$

$$(R = C_6H_5, \ C_4H_9, \ OH)$$
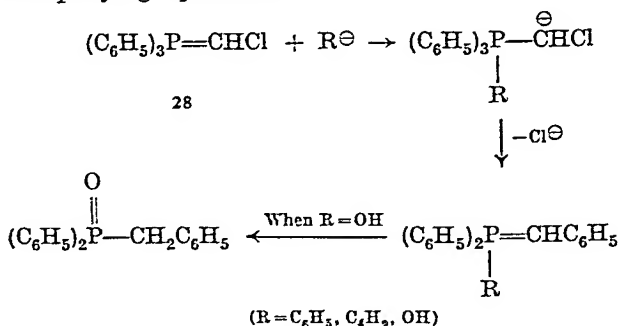
Methylene phosphoranes in which one hydrogen atom of the methylene group is replaced by an alkoxide group decompose in an even more complicated way. The autodecomposition of n-butoxymethylenetriphenylphosphorane (29) gave, in addition to triphenylphosphine as the main product, and depending on the conditions, varying amounts of 1,2-di-n-butoxyethylene, di-n-butoxymethane, 1-butene, and n-butanol.[87]

$$(C_6H_5)_3P{=}CHOC_4H_9{-}n \ \xrightarrow[\text{20 hr.}]{\text{Ether, 45}^\circ}$$
29

$$\begin{cases} (C_6H_5)_3P \ + \ n\text{-}C_4H_9OCH{=}CHOC_4H_9{-}n \ + \\ \quad (64\%) \hspace{3cm} (16\%) \\ CH_2(OC_4H_9{-}n)_2 \ + \ C_2H_5CH{=}CH_2 \ + \ n\text{-}C_4H_9OH \\ \quad (2.4\%) \hspace{2cm} (1.5\%) \hspace{2cm} (12\%) \end{cases}$$
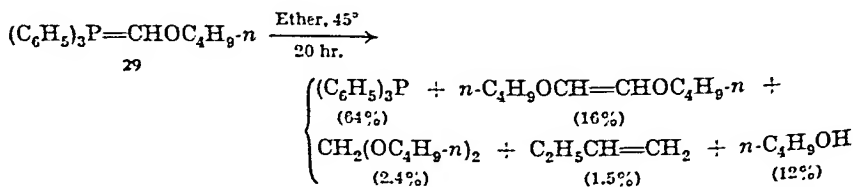
The mechanism has not been elucidated, but it has been suggested that the phosphorane 29 decomposes initially into triphenylphosphine and n-butoxycarbene. t-Butoxymethylenetriphenylphosphorane (30) and diphenoxymethylenetriphenylphosphorane (31) decompose in an essentially analogous manner.[87]

$$(C_6H_5)_3P{=}CHOC(CH_3)_3 \hspace{3cm} (C_6H_5)_3P{=}C(OC_6H_5)_2$$
$$\hspace{1cm} 30 \hspace{6cm} 31$$
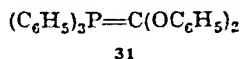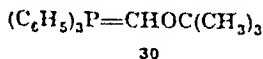
Even these phosphoranes, however, may be used in a Wittig reaction by operating at a sufficiently low temperature so that their rate of decomposition is slow.

So far only methods for the preparation of alkylidene phosphoranes which use phosphonium salts as starting materials have been mentioned. There are, however, other theoretically very interesting ways of preparation which do not start with phosphonium salts. The first alkylidene

[87] Wittig and Boll, *Chem. Ber.*, 95, 2526 (1962).

phosphorane 1 was obtained by the thermal decomposition of the phosphazine 2.[7,8] The applicability of this method remained limited, however,

$$(C_6H_5)_3P + (C_6H_5)_2CN_2 \longrightarrow$$

$$(C_6H_5)_3P{=}N{-}N{=}C(C_6H_5)_2 \xrightarrow{190°} (C_6H_5)_3P{=}C(C_6H_5)_2$$
$$\qquad\qquad\qquad 2 \qquad\qquad\qquad\qquad\qquad 1$$
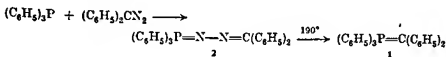
since thermal elimination of nitrogen usually occurs at temperatures at which the phosphoranes are unstable. Even the similarly resonance-stabilized fluorenylidenetriphenylphosphorane (11) could not be prepared by this route.[88] The action of diazomethane on triphenylphosphine in ethereal solution gives formaldehyde triphenylphosphazine (32),[3] which at elevated temperatures decomposes into the starting materials.

$$(C_6H_5)_3P + CH_2N_2 \rightleftharpoons (C_6H_5)_3P{=}N{-}N{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad 32$$
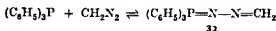
The preparation of methylenetriphenylphosphorane from diazomethane did, however, succeed under the catalytic influence of metal salts such as cuprous chloride[89] in the presence of triphenylphosphine.[90]

$$(C_6H_5)_3P + CH_2N_2 \xrightarrow{Cu^{\oplus}} (C_6H_5)_3P{=}CH_2 + N_2$$
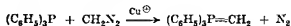
Similarly other diazo compounds such as phenyldiazomethane, diazoacetic ester, or diazoacetophenone have been converted to the corresponding ylides. Since the ylides can undergo side reactions with excess diazo compound, it is best to generate them in the presence of carbonyl compounds if they are to be used for the preparation of olefins.

The addition of carbenes to triphenylphosphine, simultaneously discovered by Wittig,[91,92] Speziale,[93,94] Seyferth,[95,96] and their co-workers, also leads to alkylidene phosphoranes which were used for the syntheses of monohalo- and 1,1-dihalo-olefins. The action of n-butyllithium on a solution of triphenylphosphine in methylene chloride at −60°, for instance, leads to chloromethylenetriphenylphosphorane.[91,92,95,96]

$$(C_6H_5)_3P + CH_2Cl_2 \xrightarrow{n\text{-}C_4H_9Li} (C_6H_5)_3P{=}CHCl$$
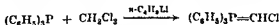
[88] Horner and Lingnau, Ann., 591, 135 (1955).
[89] Wittig and Schwarzenbach, Angew. Chem., 71, 652 (1959). Ann., 650, 1 (1961).
[90] Wittig and Schlosser, Tetrahedron, 18, 1023 (1962).
[91] Wittig and Schlosser, Angew. Chem., 72, 324 (1960).
[92] Wittig and Schlosser, Chem. Ber., 94, 1373 (1961)
[93] Speziale, Marco, and Ratts, J. Am Chem. Soc., 82, 1260 (1960)
[94] Speziale and Ratts, J. Am. Chem. Soc., 84, 854 (1962).
[95] Seyferth, Grim, and Read, J. Am Chem Soc., 82, 1510 (1960).
[96] Seyferth, Grim, and Read, J. Am. Chem. Soc., 83, 1617 (1961).

In an analogous manner dihalomethylene triphenylphosphoranes were prepared from triphenylphosphine, haloform, and potassium t-butoxide in heptane.[93,94] The preparation of difluoromethylenetriphenylphos-

$$(C_6H_5)_3P \ + \ CHX_3 \ \xrightarrow[\text{(X = Cl, Br)}]{\text{KOC}_4\text{H}_9\text{-}t} \ (C_6H_5)_3P{=}CX_2$$
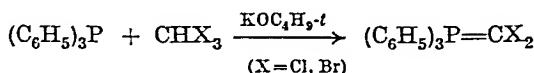
phorane[97] by a similar method could not be reproduced.[94]

Dihalomethylene triphenylphosphoranes can also be prepared in good yields by the action of triphenylphosphine on tetrahalomethanes. Heating a mixture of triphenylphosphine, carbon tetrachloride, and benzophenone to 60° for 4 hours, for instance, gave 1,1-diphenyl-2,2-dichloroethylene (33) in 78% yield.[82,98]

$$2(C_6H_5)_3P \ + \ CCl_4 \ \rightarrow \ (C_6H_5)_3P{=}CCl_2 \ + \ (C_6H_5)_3PCl_2$$

$$(C_6H_5)_3P{=}CCl_2 \ + \ (C_6H_5)_2C{=}O \ \rightarrow \ \underset{\text{33}}{(C_6H_5)_2C{=}CCl_2} \ + \ (C_6H_5)_3PO$$

$$2(C_6H_5)_3P \ + \ BrCCl_3 \ \rightarrow \ (C_6H_5)_3P{=}CCl_2 \ + \ (C_6H_5)_3PBrCl$$

$$2(C_6H_5)_3P \ + \ Cl_2CF_2 \ \rightarrow \ (C_6H_5)_3P{=}CF_2 \ + \ (C_6H_5)_3PCl_2$$

$$2(C_6H_5)_3P \ + \ CBr_4 \ \rightarrow \ (C_6H_5)_3P{=}CBr_2 \ + \ (C_6H_5)_3PBr_2$$
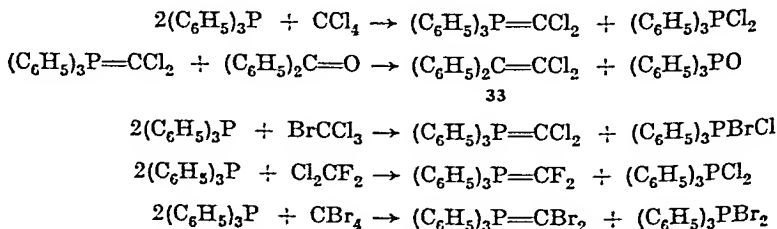
Similarly, tetrabromomethane reacts with triphenylphosphine in methylene chloride to give dibromomethylenetriphenylphosphorane, which was trapped with benzaldehyde to give β,β-dibromostyrene in 84% yield.[82]

$$(C_6H_5)_3P{=}CBr_2 \ + \ C_6H_5CHO \ \rightarrow \ C_6H_5CH{=}CBr_2 \ + \ (C_6H_5)_3PO$$

Benzoquinone and triphenylphosphine readily combine to give the yellow-green resonance-stabilized phosphorane 34.[99]

34
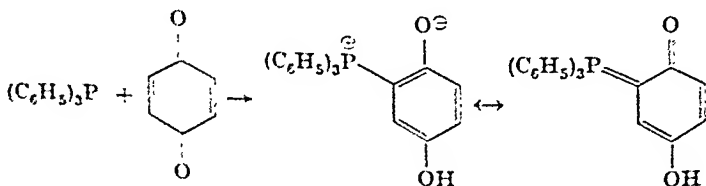
Another method for the preparation of resonance-stabilized alkylidene phosphoranes uses triphenylphosphine dichloride as a starting material.[45]

$$(C_6H_5)_3PCl_2 + CH_2 \xrightarrow[\text{Y}]{\text{X}} \xrightarrow{(C_2H_5)_2N} (C_6H_5)_3P=C \xrightarrow[\text{Y}]{\text{X}}$$

$$(X, Y = CO_2R, CN, COCH_3, SO_2C_6H_5)$$
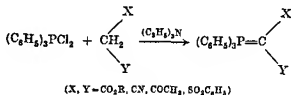
Finally, the phosphocyanine dye 35,[100] a resonance-stabilized phosphorane, may be considered to be a substituted vinylog of the mono ylide 26.

$$2(C_6H_5)_3\overset{\oplus}{P}-CH_2CO_2C_2H_5 + (C_2H_5O)_2CHCH_2CH(OC_2H_5)_2$$
$$\overset{|}{Cl\ominus}$$

$$\Big\downarrow \overset{C_6H_5N}{NaClO_4}$$

$$(C_6H_5)_3P=C-CH=CH-CH=C-\overset{\oplus}{P}(C_6H_5)_3 \quad ClO_4\ominus$$
$$\overset{|}{CO_2C_2H_5} \qquad\qquad \overset{|}{CO_2C_2H_5}$$

$$35$$
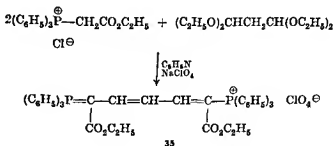
Reactions of Alkylidene Phosphoranes

Some of the reactions of the Wittig reagents reflect their markedly basic properties. All ylides react with acids to form phosphonium salts.[1]

$$(C_6H_5)_3P=CH_2 + HCl \rightarrow (C_6H_5)_3\overset{\oplus}{P}-CH_3$$
$$\overset{|}{Cl\ominus}$$
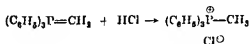
Similarly, hydrolysis[1] of unstable alkylidene phosphoranes gives phosphonium hydroxides which usually decompose irreversibly into a phosphine oxide and a hydrocarbon.[101] The most electronegative group is always removed from phosphorus.

$$(C_6H_5)_3P=CH_2 \xrightarrow{H_2O} (C_6H_5)_3\overset{\oplus}{P}-CH_3 \longrightarrow (C_6H_5)_3\overset{O}{\overset{||}{P}}CH_3 + C_6H_6$$
$$\overset{|}{HO\ominus}$$
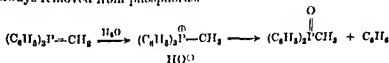
[100] Kukhtin, Kasymov, and Voskoboeva, *Dokl. Akad. Nauk SSSR*, **140**, 601 (1961).
[101] Fenton and Ingold, *J. Chem. Soc.*, **1929**, 2342

In order to hydrolyze resonance-stabilized alkylidene phosphoranes it is necessary to apply elevated temperatures and to use aqueous or alcoholic solutions of alkali metal hydroxides, as shown in the example of fluorenylidenetriphenylphosphorane (11).[49]
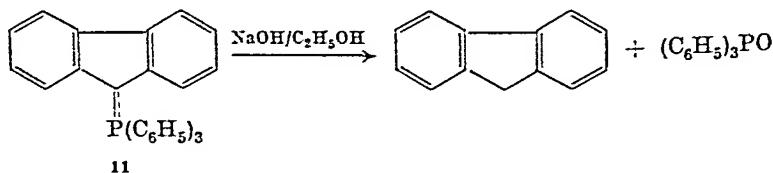
Hydrolysis of acylalkylidene triphenylphosphoranes[31,32] gives ketones; of carbomethoxyalkylidene triphenylphosphoranes,[40] carboxylic acids. In

$$(C_6H_5)_3P{=}CCOR' \xrightarrow[\text{HO}^{\ominus}]{\text{H}_2\text{O}} (C_6H_5)_3PO + RCH_2COR'$$
$$\overset{|}{R}$$

$$(C_6H_5)_3P{=}CCO_2CH_3 \xrightarrow[\text{HO}^{\ominus}]{2\text{H}_2\text{O}} (C_6H_5)_3PO + RCH_2CO_2H + CH_3OH$$
$$\overset{|}{R}$$
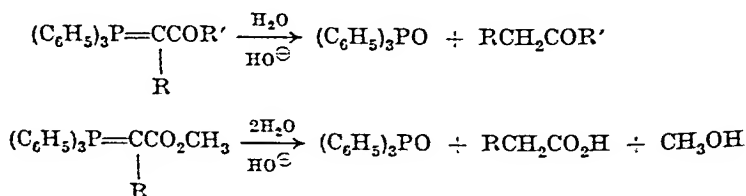
certain cases, phosphonium hydroxides are quite stable. Hexaphenylcarbodiphosphorane (27), for instance, dissolves readily in water to give a strong diacidic base (36) that can be titrated with hydrochloric acid. The elimination of benzene with the formation of a new ylene 37 which is stabilized by a phosphoryl group occurs only very slowly.[61]
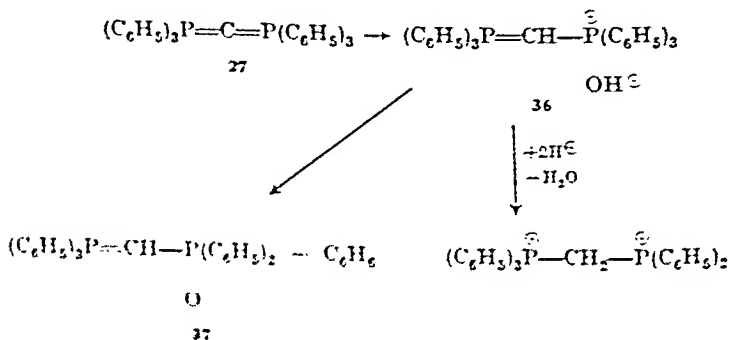
The addition of alkyl halides to alkylidene phosphoranes leads to phosphonium halides.[51,102]

$$(CH_3)_3P\text{=}CH_2 + CH_3I \rightarrow (CH_3)_3\overset{\oplus}{P}\text{—}CH_2CH_3$$
$$I^{\ominus}$$
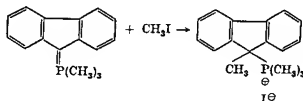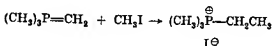
Similarly, trialkyloxonium fluoborates give the corresponding phosphonium fluoborates.[102,103]

$$(C_6H_5)_3P\text{=}CHC_6H_5 + (C_2H_5)_3\overset{\oplus}{O}\overset{\ominus}{B}F_4 \rightarrow (C_6H_5)_3\overset{\oplus}{P}\text{—}\overset{C_2H_5}{\underset{BF_4^{\ominus}}{\text{—}CHC_6H_5}}$$
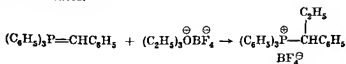
Resonance-stabilized ylides are not necessarily attacked on the α-carbon atom. Acylmethylene triphenylphosphoranes, for instance, are alkylated on oxygen.[31]

$$(C_6H_5)_3P\text{=}CH\text{—}CR + C_2H_5I \rightarrow (C_6H_5)_3\overset{\oplus}{P}\text{—}CH\text{=}CR$$
$$\underset{O}{|} \qquad\qquad I^{\ominus} \quad \underset{OC_2H_5}{|}$$
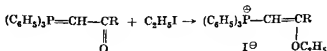
Carbomethoxymethylenetriphenylphosphorane, on the other hand, is alkylated on carbon.[40,104]

$$(C_6H_5)_3P\text{=}CHCO_2CH_3 + RX \rightarrow (C_6H_5)_3\overset{\oplus}{P}\text{—}\overset{}{\underset{X^{\ominus}\ R}{\text{—}CHCO_2CH_3}}$$
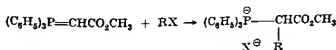
An electron-withdrawing group, R, will increase the acidity of the newly formed phosphonium salt relative to that of the unsubstituted one, and the salt therefore reacts with excess starting ylide by *trans* ylidation with

[101] Wittig and Rieber, *Ann.*, 562, 177 (1949).
[103] Märkl, *Tetrahedron Letters*, 1962, 1027.
[104] Bestmann and Schulz, *Tetrahedron Letters*, 4, 5 (1960).

formation of a new phosphorane.[16,105]

$$(C_6H_5)_3\overset{\ominus}{P}\text{——CHCO}_2CH_3 \;+\; (C_6H_5)_3P\text{=CHCO}_2CH_3$$
$$X\ominus \quad R$$

$$\Updownarrow$$

$$(C_6H_5)_3P\text{=CCO}_2CH_3 \;+\; (C_6H_5)_3\overset{\ominus}{P}CH_2CO_2CH_3$$
$$R \qquad\qquad X\ominus$$

The substituted carbomethoxymethylene phosphoranes yield, on hydrolysis, carboxylic acids in which the carbon chain of the alkyl halide used for the alkylation has been extended by two carbon atoms. The result is similar to that of a malonic ester synthesis.

If phenacyl bromide or other α-bromo ketones are used as alkylating agents, the initially formed phosphonium salt undergoes a Hofmann elimination instead of *trans*ylidation, with the formation of α,β-unsaturated γ-ketonic esters.[106]

$$(C_6H_5)_3\overset{\ominus}{P}\text{——CH——CO}_2CH_3 \;+\; (C_6H_5)_3P\text{=CHCO}_2CH_3$$
$$Br\ominus$$
$$H\text{——CH——COC}_6H_5$$

$$\downarrow$$

$$(C_6H_5)_3P \;+\; \begin{matrix} CHCO_2CH_3 \\ \| \\ CHCOC_6H_5 \end{matrix} \;+\; (C_6H_5)_3\overset{\ominus}{P}\text{——CH}_2CO_2CH_3$$
$$Br\ominus$$

Similarly the reaction of phenacyl bromide with benzoylmethylenetriphenylphosphorane gives mainly *trans*-dibenzoylethylene (38); the formation of some *trans*-tribenzoylcyclopropane (39) in this reaction led to the proposal of a carbene mechanism.[107,108]

$$(C_6H_5)_3P\text{=CHCOC}_6H_5 \;+\; C_6H_5COCH_2Br \rightarrow [C_6H_5COCH:] \;+\; (C_6H_5)_3\overset{\ominus}{P}CH_2COC_6H_5$$
$$Br\ominus$$

$$C_6H_5COCH\text{=CHCOC}_6H_5 \xrightarrow{[C_6H_5COCH:]} \begin{matrix} COC_6H_5 \quad COC_6H_5 \end{matrix}$$
$$\underset{38}{} \qquad\qquad\qquad COC_6H_5$$
$$39$$

The postulation of carbene intermediates is not necessary since, as will be shown later, ylides are capable of adding to activated double bonds with the formation of cyclopropane derivatives. Phosphoranes containing halogen atoms can undergo an intramolecular carbon alkylation[74,109] and may thus be used for the synthesis of cyclic compounds such as phenanthrene.[109]
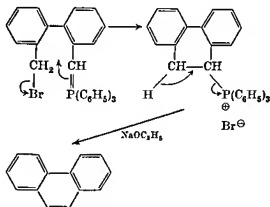
Alkylidene phosphoranes react readily with acid chlorides. The initially formed phosphonium salts undergo *trans* ylidation very easily owing to the strongly electron-withdrawing effect of the acyl group.[32,41,58,110]

$$(C_6H_5)_3P{=}CHR + R'COCl \rightarrow (C_6H_5)_3\overset{\oplus}{P}{-}CHR$$
$$\underset{(C_6H_5)_3P=CHR}{\downarrow} \qquad \underset{COR'}{\overset{Cl^\ominus}{|}}$$

$$(C_6H_5)_3P{=}CR + (C_6H_5)_3\overset{\oplus}{P}CH_2R$$
$$\underset{COR'}{|} \qquad\qquad Cl^\ominus$$
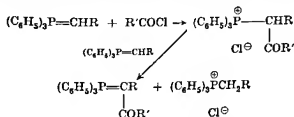
Strongly basic ylides may eliminate hydrogen chloride from acid chlorides containing activated α-hydrogen atoms (e.g., phenylacetyl chloride). The ketenes so formed react with the alkylidene phosphoranes to give allenes.[32]

Chloroformic esters and alkylidene triphenylphosphoranes react to give carbalkoxymethylene triphenylphosphoranes.[111]

$$2(C_6H_5)_3P{=}CHR + ClCO_2CH_3 \rightarrow$$
$$(C_6H_5)_3P{=}CRCO_2CH_3 + (C_6H_5)_3\overset{\oplus}{P}{-}CH_2R$$
$$Cl^\ominus$$
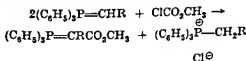
[109] Bestmann and Häberlein, *Z. Naturforsch.*, **17b**, 787 (1962).
[110] Bestmann, *Tetrahedron Letters*, **4**, 7 (1960).
[111] Bestmann and Schulz, *Angew. Chem.*, **73**, 27 (1961).

In a reaction similar to that of acid chlorides, carboxylic esters react with alkylidene phosphoranes with the formation of phosphonium alkoxides.[2]

$$(C_6H_5)_3P{=}CH_2 \; + \; C_6H_5CO_2C_2H_5 \; \rightarrow \; (C_6H_5)_3\overset{\oplus}{P}{-}CH_2COC_6H_5$$

$$\ominus OC_2H_5$$

$$(C_6H_5)_3P{=}CHCOC_6H_5 \; + \; C_2H_5OH$$
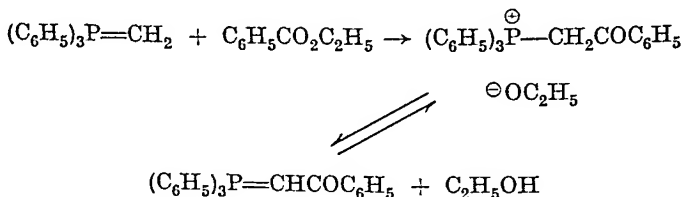
Using thiocarboxylic acid S-ethyl esters, a convenient method for the preparation of acylalkylidene triphenylphosphoranes was developed.[32,112] Removal of the volatile mercaptan shifts the equilibrium from the initially formed phosphonium ethyl mercaptide completely to the side of the corresponding ylene. Compared with the acylation with acid

$$(C_6H_5)_3P{=}CHR \; + \; R'COSC_2H_5 \; \rightarrow \; (C_6H_5)_3\overset{\oplus}{P}{-\!-}CHR$$

$$C_2H_5S^{\ominus} \quad COR'$$

$$(C_6H_5)_3P{=}CRCOR' \; + \; C_2H_5SH$$
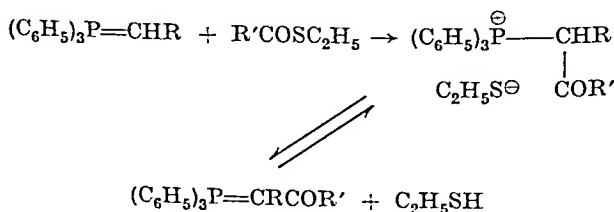
chlorides, this method has the advantage that the components may be used in a 1:1 ratio since deprotonation of the initially formed phosphonium salt is carried out by mercaptide ion and not by an excess of the starting ylene. In addition, the possibility of ketene formation is reduced, and, consequently, the yields are usually considerably higher.

With formic esters, which may be considered to contain both an aldehyde and an ester function, phosphoranes react to give different products depending on the conditions used. Adding an ylide to an excess of ethyl formate results in the normal ester reaction products, in this case formylethylidenetriphenylphosphorane.[33,58]

$$(C_6H_5)_3P{=}CHR \; + \; HCO_2C_2H_5 \; \rightarrow$$

$$(C_6H_5)_3\overset{\ominus}{P}{-\!-}CHR \; \rightleftharpoons \; (C_6H_5)_3P{=}CR \; + \; C_2H_5OH$$

$$C_2H_5O^- \quad CHO \qquad\qquad CHO$$
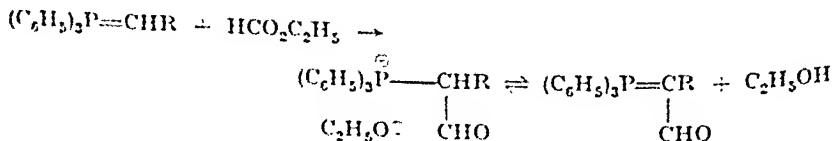
[112] Bestmann and Arnason, *Tetrahedron Letters*, 1961, 455.

Inverse addition, on the other hand, yields the products of a Wittig reaction, namely, an enol ether and triphenylphosphine oxide.[113]

$$(C_6H_5)_3P = \bigcirc \quad + \quad HCO_2C_2H_5 \quad \rightarrow \quad \bigcirc = CHOC_2H_5 \quad + \quad (C_6H_5)_3PO$$
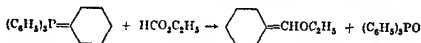
An explanation for these differing results may possibly be found in a solvation of the positively charged phosphorus by excess formic ester. In the first case, such a solvation might preclude the Wittig reaction by making a nucleophilic attack of the oxygen on phosphorus impossible; the zwitterion 40, which is probably initially formed, therefore collapses in a different way. Support for this explanation is found in the fact that

$$(C_6H_5)_3PO \ + \ \begin{matrix} CHR \\ \| \\ CHOC_2H_5 \end{matrix} \quad \begin{matrix} (C_6H_5)_3\overset{+}{P}-CHR \\ | \\ \Theta O-CHOC_2H_5 \end{matrix} \quad \rightarrow \quad \begin{matrix} (C_6H_5)_3\overset{\oplus}{P}-CHR \\ | \\ C_2H_5O\Theta \quad CHO \end{matrix}$$

$$40$$
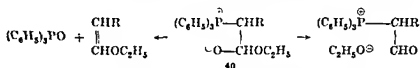
lithium bromide, which is known to shield phosphorus by complex formation,[114] increases the yields in the above-mentioned reaction of alkylidene phosphoranes with normal esters[32] in which a side reaction involving attack of the oxygen on phosphorus must also be expected.

The imidazolides, which are related to acid chlorides and esters, have been found to be particularly useful in the preparation of acylalkylidene triphenylphosphoranes.[115]

$$2(C_6H_5)_3P = CHR \ + \ R'COIm \ \rightarrow \ (C_6H_5)_3P = CRCOR' \ + \ (C_6H_5)_3\overset{\oplus}{P}-CH_2R$$

$$Im\Theta$$

$$\left(Im = \begin{matrix} \fbox{N} \\ N \end{matrix} \right)$$
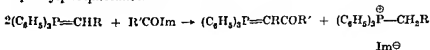
Using N-formylimidazole, the corresponding formylalkylidene triphenyl-phosphoranes (41) are obtained; with N,N'-carbonyldiimidazole, carbo-imidazolidoalkylidene triphenylphosphoranes (42)[116] are formed.

$$(C_6H_5)_3P = CHR$$

$$(C_6H_5)_3P = CRCHO \qquad\qquad (C_6H_5)_3P = CRCOIm$$
$$41 \qquad\qquad\qquad\qquad\qquad 42$$
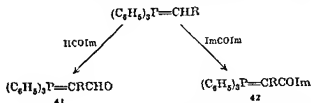
[113] Pommer and Wittig, Ger. pat. 1,047,763 (to BASF) (*Chem. Zentr.*, 1959, 13577).

[114] Bergelson and Shemyakin, *Tetrahedron*, 19, 149 (1963).

[115] Bestmann, Sommer, and Staab, *Angew. Chem.*, 74, 293 (1962).

[116] Staab and Sommer, *Angew. Chem.*, 74, 294 (1962).

The interaction of halogens with resonance-stabilized ylides, such as carbomethoxymethylenetriphenylphosphorane and acylmethylene triphenylphosphoranes, gives halogenated alkylidene phosphoranes.[59,60,117]

$$(C_6H_5)_3P=CHCOR + X_2 \longrightarrow$$

$$\overset{\oplus}{(C_6H_5)_3P}-CHXCOR \xrightarrow{-HX} (C_6H_5)_3P=CXCOR$$

$$X^{\ominus}$$

$$(X=Cl, Br, I; R=CH_3O, C_2H_5O, CH_3, C_6H_5)$$

The use of iodobenzene dichloride[59,117] or t-butyl hypochlorite[60] in place of chlorine has been found to be advantageous. Elimination of hydrogen halide is effected either by *trans* ylidation using excess phosphorane or by addition of bases such as sodium hydroxide, triethylamine, or pyridine.

The reaction with halogens is not limited to resonance-stabilized alkylidene phosphoranes, as is shown by the reaction of dibromomethylenetriphenylphosphorane with bromine, which leads to a product that cannot eliminate hydrogen halide.[82]

$$(C_6H_5)_3P=CBr_2 + Br_2 \rightarrow \overset{\ominus}{(C_6H_5)_3P}-CBr_3$$

$$Br^{\ominus}$$

Hexaphenylcarbodiphosphorane (27) also reacts readily with bromine in methylene chloride.[61]

$$(C_6H_5)_3P=C=P(C_6H_5)_3 + Br_2 \rightarrow (C_6H_5)_3P=C\overset{\oplus}{-P}(C_6H_5)_3$$

$$\underset{Br\ \ Br^{\ominus}}{|}$$

27

Interaction of acylated carbomethoxymethylene triphenylphosphoranes with phosphorus pentachloride or Vilsmeier reagents, on the other hand, gives phosphonium salts halogenated in the β-position to the phosphorus atom.[118] Hydrolysis of these products gives alkyne carboxylic acids.

$$Cl^{\ominus}$$

$$(C_6H_5)_3\overset{\ominus}{P}-C-CO_2CH_3 \xrightarrow{PCl_5} (C_6H_5)_3\overset{\oplus}{P}-C-CO_2CH_3 \xrightarrow[NaOH]{H_2O}$$

$$\underset{CO-C-R}{|} \qquad\qquad \underset{Cl-C-R}{|}$$

$$(C_6H_5)_3PO + RC\equiv CCO_2H + CH_3OH + HCl$$

Phosphonium salts substituted by phosphorus on the α-carbon atom are obtained in the reaction of alkylidene triphenylphosphoranes with

[117] Märkl, *Chem. Ber.*, **94**, 2996 (1961).
[118] Märkl, *Angew. Chem.*, **74**, 217 (1962).

phenyldibromophosphine, diphenylbromophosphine,[110] or triphenylphosphine dibromide.[82]

Metalloidal, tin, and mercury halides undergo an interesting nucleophilic displacement of halide ion under the influence of ylides.[120–122] The products are phosphonium salts substituted on the α-carbon atom by metalloids, tin, or mercury.

$$(C_6H_5)_3P{=}CH_2 + (CH_3)_3SiBr \rightarrow (C_6H_5)_3\overset{\oplus}{P}CH_2Si(CH_3)_3$$
$$Br^{\ominus}$$
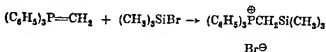
Alkylidene phosphoranes are also capable of cleaving silicon-silicon bonds; for instance, methylenetriphenylphosphorane reacts with octaphenylcyclotetrasilane with opening of the ring.[123]

Metals may be used as reducing agents for ylides. Thus zinc in acetic acid converts acylmethylene triphenylphosphoranes to ketones and triphenylphosphine.[88]

$$(C_6H_5)_3P{=}CHCOC_6H_5 \xrightarrow[CH_3CO_2H]{Zn} (C_6H_5)_3P + CH_3COC_6H_5$$
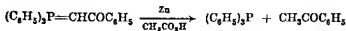
The same result is obtained with Raney nickel, but triphenylphosphine is unstable toward Raney nickel and cannot be isolated.[124]
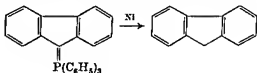
Reduction of ylides with lithium aluminum hydride takes a different course. One phenyl group is removed from phosphorus with the formation of benzene.[125]

$$(C_6H_5)_3P{=}CHCOC_6H_5 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} (C_6H_5)_2PCH_2COC_6H_5 + C_6H_6$$
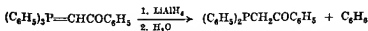
The reactive alkylidene phosphoranes are easily oxidized. They are so sensitive to oxygen that their preparation has to be carried out in an inert atmosphere. Oxidation leads, initially, to triphenylphosphine oxide and a carbonyl compound; the latter undergoes a Wittig reaction with

[119] Seyferth and Brändle, *J. Am. Chem. Soc.,* 83, 2055 (1961)

[120] Grim and Seyferth, *Chem. Ind (London),* 1959, 849.
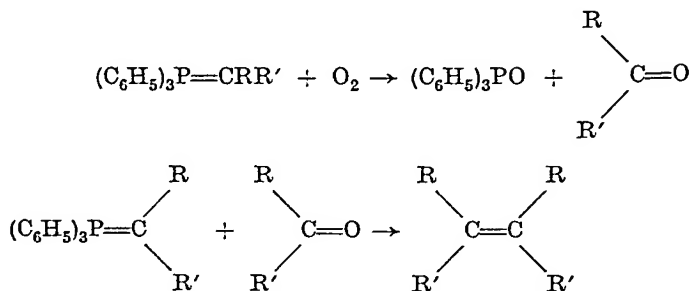
[121] Seyferth, *Angew. Chem.,* 72, 36 (1960).

[122] Seyferth and Grim, *J. Am. Chem. Soc.,* 83, 1610 (1961).

[123] Gilman and Tomasi, *J. Org. Chem.,* 27, 3647 (1962).

[124] Schönberg, Brosowski, and Singer, *Chem. Ber.,* 95, 2984 (1962).

[125] Saunders and Burchman, *Tetrahedron Letters,* 1, 8 (1959).

unoxidized ylide to form the symmetrical olefin in which both halves come from the alkylidene phosphorane.[126,127]

$$(C_6H_5)_3P{=}CRR' + O_2 \rightarrow (C_6H_5)_3PO + \underset{R'}{\overset{R}{>}}C{=}O$$

$$(C_6H_5)_3P{=}C\underset{R'}{\overset{R}{<}} + \underset{R'}{\overset{R}{>}}C{=}O \rightarrow \underset{R'}{\overset{R}{>}}C{=}C\underset{R'}{\overset{R}{<}}$$

By this method, vitamin A was converted to β-carotene (44) via axerophthylenetriphenylphosphorane (43).[128]

43

44
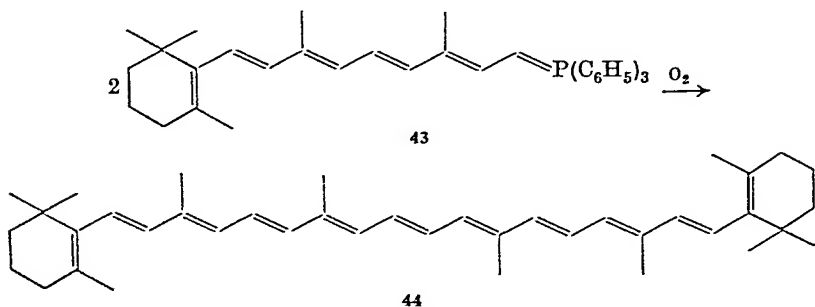
Oxidation of bifunctional ylides may lead to ring closure[127] as, for instance, in a synthesis of phenanthrene. Peracetic acid can be used
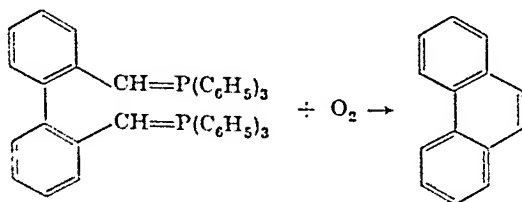
instead of oxygen as the oxidizing agent.[129] This reagent is also capable of oxidizing the resonance-stabilized ylides such as acylalkylidene and carbalkoxyalkylidene triphenylphosphoranes.

Staudinger found that, in analogy to its oxidation, diphenylmethylene-triphenylphosphorane reacts with elemental sulfur to give triphenyl-phosphine sulfide and thiobenzophenone. Because of the low reactivity of the phosphorane, a further reaction did not take place.[8]

$$(C_6H_5)_3P=C(C_6H_5)_2 + 2S \rightarrow (C_6H_5)_3PS + (C_6H_5)_2C=S$$

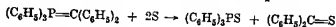In their capacity as nucleophiles, alkylidene phosphoranes can add to activated double bonds. Depending on the nature of the substituent, the initially formed zwitterion 45 can stabilize itself in three different ways.
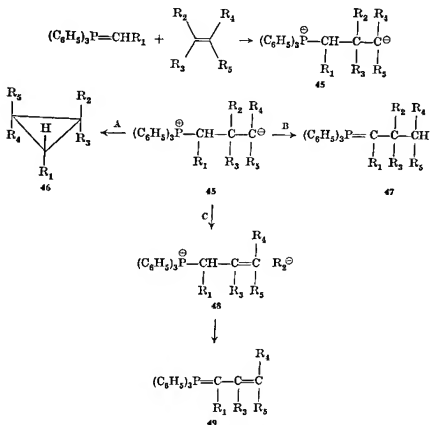
Formation of a cyclopropane derivative 46[130][131] by elimination of tri-phenylphosphine (path A) is preferred if R_1 is a group which is not electron-withdrawing, e.g., hydrogen or alkyl.[132] This is illustrated by

[130] Mechoulam and Sondheimer, *J. Am. Chem. Soc.*, 80, 4386 (1958).

[131] Freeman, *Chem. Ind.* (*London*), 1959, 1254.

[132] Bestmann and Seng, *Angew. Chem.*, 74, 154 (1962).

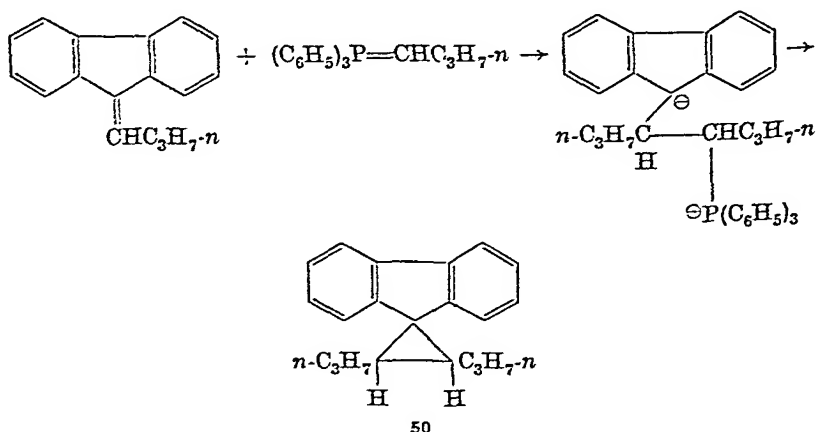the reaction of 9-*n*-butylidenefluorene with *n*-butylidenetriphenyl-phosphorane, which yields the spiro compound **50**.[130]

50

Michael addition of the alkylidene phosphorane to the double bond to form the new ylide **47** (path B) occurs preferentially if R_1 is an electron-withdrawing group capable of resonance interaction.[132]

$$(C_6H_5)_3P = CHCO_2CH_3 + C_6H_5COCH = CHCO_2CH_3 \rightarrow$$

$$(C_6H_5)_3P = C - \overset{\displaystyle COC_6H_5}{\underset{\displaystyle CO_2CH_3}{\overset{\displaystyle |}{\underset{|}{C}}}HCH_2CO_2CH_3}$$
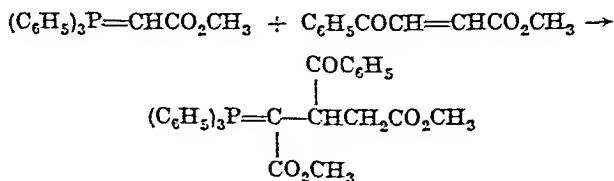
Path C is possible only if R_2 or R_3 are substituents capable of forming stable anions such as ethoxide or cyanide.[123]

$$(C_6H_5)_3P = CHCN + C_2H_5OCH = C(CO_2C_2H_5)_2 \rightarrow$$

$$(C_6H_5)_3P = C - CH = C(CO_2C_2H_5)_2 + C_2H_5OH$$
$$\underset{CN}{|}$$
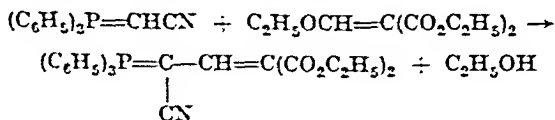
As expected, the Wittig reagents add to the electrophilic derivatives of trivalent boron, such as boron hydrides,[134,135] boron halides,[120,121,135] and triphenylboron.[126-128]

$$2(C_6H_5)_3P{=}CHR + B_2H_6 \rightarrow 2(C_6H_5)_3\overset{\oplus}{P}{-}CHR\overset{\ominus}{B}H_3$$

$$(C_6H_5)_3P{=}CH_2 + (CH_3)_3\overset{\ominus}{N}{-}\overset{\ominus}{B}H_3 \rightarrow (C_6H_5)_3\overset{\oplus}{P}{-}CH_2\overset{\ominus}{B}H_3$$

$$\uparrow\text{LiAlH}_4$$

$$(C_6H_5)_3P{=}CH_2 + BF_3 \rightarrow (C_6H_5)_3\overset{\oplus}{P}{-}CH_2\overset{\ominus}{B}F_3$$

$$\downarrow\text{C}_6\text{H}_5\text{MgX}$$

$$(C_6H_5)_3P{=}CH_2 + B(C_6H_5)_3 \rightarrow (C_6H_5)_3\overset{\oplus}{P}{-}CH\overset{\ominus}{B}(C_6H_5)_3$$
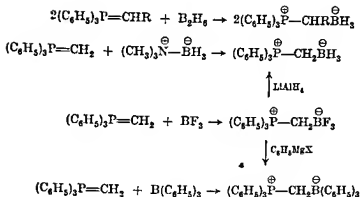
The reactions of alkylidene phosphoranes with a number of diazo compounds and diazonium salts are also of interest. Even the relatively unreactive cyclopentadienylidenetriphenylphosphorane (10) is readily attacked by benzenediazonium chloride. Strikingly, addition does not occur on the ylide carbon but in the 2-position, giving rise to the longest possible conjugated system.[139-141] The other resonance-stabilized Wittig
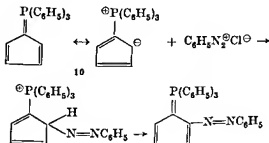
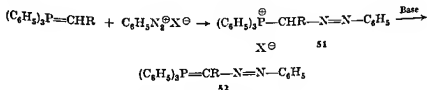reagents are attacked by diazonium salts in the normal fashion on the α-carbon atom.[142,143] The arylazoalkylphosphonium salts 51 so obtained can be converted with bases to arylazoalkylidene triphenylphosphoranes (52).

$$(C_6H_5)_3P{=}CHR + C_6H_5\overset{\oplus}{N}_2X^{\ominus} \rightarrow \underset{X^{\ominus}\quad\quad 51}{(C_6H_5)_3\overset{\oplus}{P}{-}CHR{-}N{=}N{-}C_6H_5} \xrightarrow{\text{Base}}$$

$$\underset{52}{(C_6H_5)_3P{=}CR{-}N{=}N{-}C_6H_5}$$
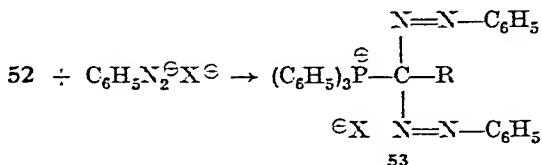
[139] Ramirez and Levy, J. Org. Chem., 21, 1333 (1956).
[140] Ramirez and Levy, J. Am. Chem. Soc., 79, 6167 (1957).
[141] Ramirez and Levy, J. Org. Chem., 23, 2035 (1958).
[142] Märkl, Tetrahedron Letters, 1961, 807.
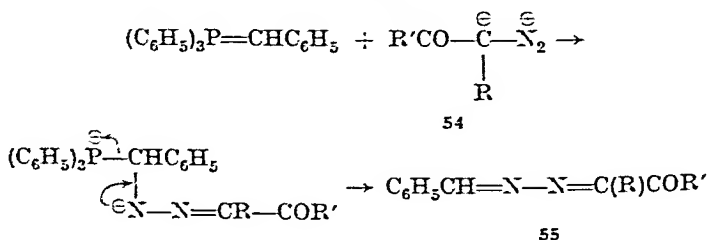[143] Märkl, Z. Naturforsch., 17b, 782 (1962).

Strongly basic ylides (e.g., $R = C_6H_5$) furnish arylazoalkylidene phosphoranes (52) by *trans* ylidation without the addition of bases. Further reaction leads to the formation of bis-arylazoalkylphosphonium salts (53).
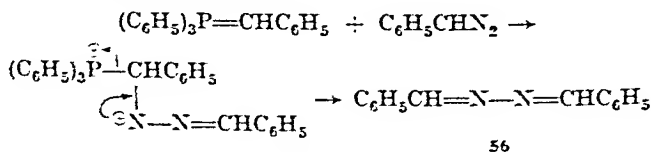
$$52 \;+\; C_6H_5N_2^{\ominus}X^{\ominus} \;\rightarrow\; (C_6H_5)_3\overset{\oplus}{P}-\underset{\underset{53}{N=N-C_6H_5}}{\overset{\overset{N=N-C_6H_5}{|}}{C}}-R \qquad {}^{\ominus}X$$

If $R = CO_2H$, subsequent elimination of carbon dioxide and hydrogen halide leads to bis-azoarylmethylene triphenylphosphoranes.[143]

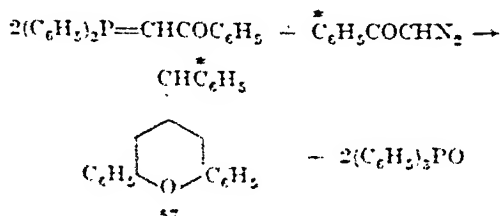From benzylidenetriphenylphosphorane and aliphatic diazo compounds of structure 54, mixed azines 55 are formed.[144]

$$(C_6H_5)_3P{=}CHC_6H_5 \;+\; R'CO-\overset{\oplus}{\underset{\underset{54}{R}}{\overset{|}{C}}}-\overset{\ominus}{N_2} \;\rightarrow$$

$$(C_6H_5)_3\overset{\ominus}{P}{-}CHC_6H_5 \atop {}_{\ominus}N{-}N{=}CR{-}COR' \qquad \rightarrow \quad C_6H_5CH{=}N{-}N{=}C(R)COR'$$

55

The same phosphorane reacts with phenyldiazomethane in a similar fashion to give benzalazine (56).[90]

$$(C_6H_5)_3P{=}CHC_6H_5 \;+\; C_6H_5CHN_2 \;\rightarrow$$

$$(C_6H_5)_3\overset{\ominus}{P}{-}CHC_6H_5 \atop {}_{\ominus}N{-}N{=}CHC_6H_5 \qquad \rightarrow \quad C_6H_5CH{=}N{-}N{=}CHC_6H_5$$

56

An unexpected result was obtained in the interaction of diazoacetophenone with benzoylmethylenetriphenylphosphorane to give the heterocyclic product 57. The only fact pertaining to the mechanism of this reaction is that the benzylidene group of the pyran derivative 57 is derived from the diazo compound.[145,146]

$$2(C_6H_5)_3P{=}CHCOC_6H_5 \;+\; \overset{*}{C}_6H_5COCHN_2 \;\rightarrow$$

$$\overset{*}{CH}C_6H_5$$

57

$+\; 2(C_6H_5)_3PO$

The reaction of benzylidenetriphenylphosphorane with phenyl azide resembles that with diazo compounds.[147] The triphenylphosphine, which is formed in addition to benzylideneaniline (58), reacts with excess phenyl azide to furnish tetraphenylphosphine imide (59).

$$(C_6H_5)_3P=CHC_6H_5 + C_6H_5N_3 \longrightarrow (C_6H_5)_3\overset{\oplus}{P}-CHC_6H_5 \xrightarrow{C_6H_5N_3}$$
$$\underset{\ominus}{NC_6H_5}$$

$$C_6H_5CH=NC_6H_5 + (C_6H_5)_3P=NC_6H_5$$
$$\qquad\quad 58 \qquad\qquad\qquad 59$$
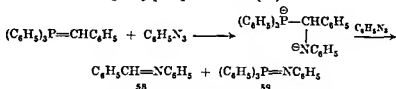
Of the further reactions of alkylidene phosphoranes, only those with carbonium and nitrilium salts will be mentioned.[103] In both cases nucleophilic attack by the ylide occurs on the carbon atom with the initial formation of substituted phosphonium salts, which may react further with bases.

The preparatively most important aspect of the alkylidene phosphoranes is without doubt their reaction with carbonyl compounds to form olefins. The details of the Wittig reaction are discussed in the next section.

MECHANISM AND STEREOCHEMISTRY

Mechanism

Definitive kinetic studies of reactions of unstabilized alkylidene phosphoranes have not yet been made. In fact, it is not possible at present to make a final statement about the mechanism of the Wittig reaction. Using the available facts, it is possible, however, to outline the path of this complex reaction.
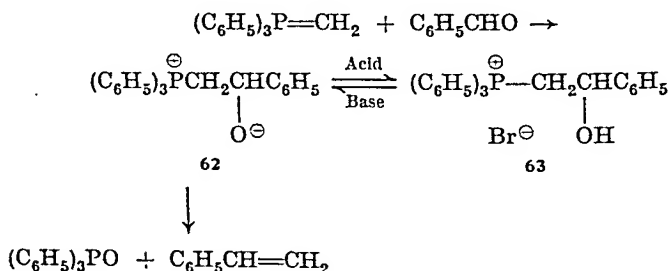
Olefin formation from alkylidene triphenylphosphoranes and carbonyl compounds occurs by way of the intermediates shown in the accompanying
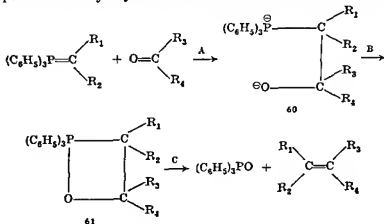
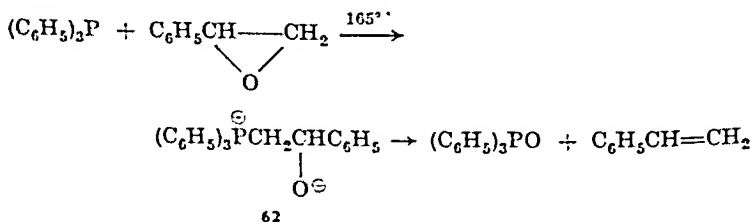147 Hoffmann, *Chem. Ber.*, 95, 2563 (1962).

formulation. In the first step, nucleophilic addition of the alkylidene phosphorane in its ylide form to the polarized carbonyl group gives the phosphonium betaine 60. As a consequence of the great affinity of phosphorus for oxygen and the possibility of expanding the valence shell of phosphorus to 10 electrons, a P—O bond is formed next, giving rise to the four-membered ring compound 61, which then collapses into triphenylphosphine oxide and an olefin.

Experimental proof for the formation of a zwitterion in step A of the reaction was obtained from the interaction of methylenetriphenylphosphorane with benzaldehyde.[2] The zwitterion 62 is stable at room temperature and may be characterized as its hydrobromide 63. The

$$(C_6H_5)_3P \!=\! CH_2 \ + \ C_6H_5CHO \ \rightarrow$$

$$(C_6H_5)_3\overset{\ominus}{P}CH_2CHC_6H_5 \underset{\text{Base}}{\overset{\text{Acid}}{\rightleftharpoons}} (C_6H_5)_3\overset{\oplus}{P}\!-\!CH_2CHC_6H_5$$

$$\underset{\overset{|}{O^{\ominus}}}{} \qquad\qquad\qquad \underset{Br^{\ominus}\quad\overset{|}{OH}}{}$$

$$\text{62} \qquad\qquad\qquad\qquad \text{63}$$

$$\downarrow$$

$$(C_6H_5)_3PO \ + \ C_6H_5CH\!=\!CH_2$$

action of phenyllithium on the β-hydroxyphosphonium salt 63 regenerates 62, which must be heated to 65° for an extended period in order to effect decomposition into triphenylphosphine oxide and styrene.

Initial formation of 62 has also been postulated for the reaction of triphenylphosphine with styrene oxide.[3] Since ring opening of the epoxide requires a temperature of 165°, the reaction proceeds directly to styrene and triphenylphosphine oxide.

$$(C_6H_5)_3P \ + \ C_6H_5CH\!\!-\!\!-\!\!CH_2 \ \xrightarrow{165°}$$
$$\underset{O}{\diagdown\diagup}$$

$$(C_6H_5)_3\overset{\ominus}{P}CH_2CHC_6H_5 \ \rightarrow \ (C_6H_5)_3PO \ + \ C_6H_5CH\!=\!CH_2$$
$$\underset{\overset{|}{O^{\ominus}}}{}$$
$$\text{62}$$

This is a general method for the conversion of epoxides to olefins. For example, cinnamic ester is obtained in 82% yield from phenylglycidic ester.

$$(C_6H_5)_3P \ + \ C_6H_5CH\!\!-\!\!-\!\!CHCO_2R \ \rightarrow \ (C_6H_5)_3PO \ + \ C_6H_5CH\!=\!CHCO_2R$$
$$\underset{O}{\diagdown\diagup}$$
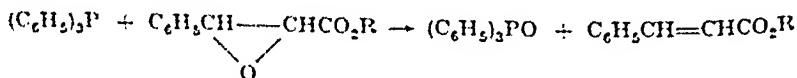
A stereochemical investigation of this deoxygenation reaction confirmed the mechanism proposed.[148] It was found that tributylphosphine reacts with *cis*-2-butene epoxide to form mainly *trans*-2-butene, whereas *trans*-2-butene epoxide gives mainly *cis*-2-butene.
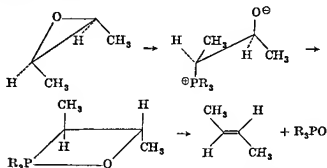
An ionic intermediate has also been proposed for the reaction of cyclic carbonates with phosphines.[149]
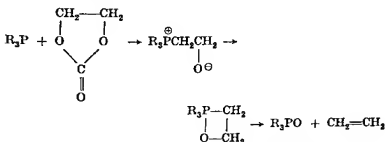
The isolation of unusually stable intermediates in a Wittig reaction has been reported recently.[150] Interaction of diphenylketene with isopropylidenetriphenylphosphorane gave a pale yellow crystalline compound, 64, which cleaved to triphenylphosphine oxide and 1,1-dimethyl-3,3-diphenyl-allene only at temperatures above its melting point (140°). Hydrogen
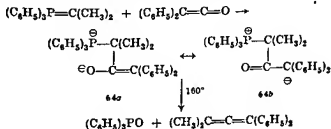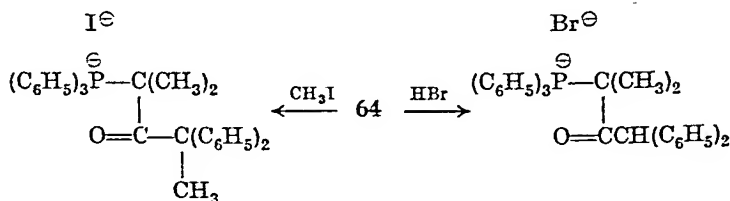
[148] Boskin and Denney, *Chem. Ind.* (*London*), 1959, 330.
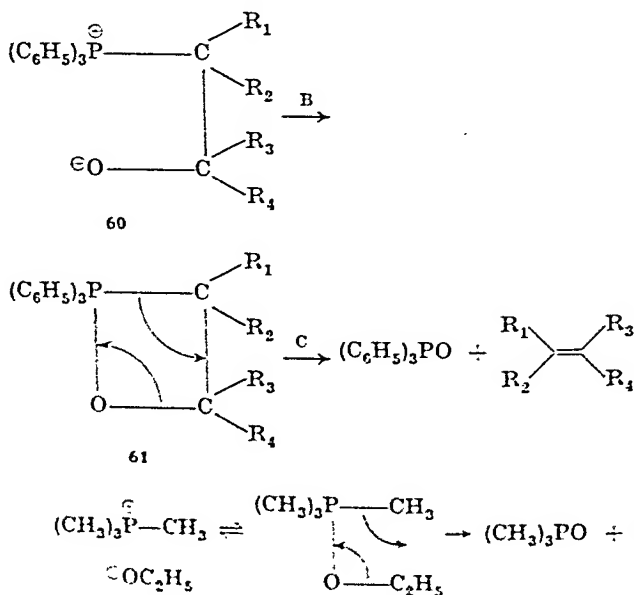[149] Keough and Grayson, *J. Org. Chem.*, 27, 1817 (1962).
[150] Wittig and Haag, *Chem. Ber.*, 96, 1535 (1963).

bromide and methyl iodide attack compound 64 on carbon. In view of the
relatively small dipole moment of 4.34 D, it cannot be said with certainty
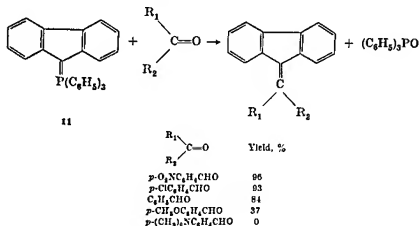
$$
I^{\ominus} \qquad\qquad\qquad\qquad\qquad\qquad Br^{\ominus}
$$

$$
(C_6H_5)_3\overset{\ominus}{P}\!\!-\!\!C(CH_3)_2 \qquad\xleftarrow{\ CH_3I\ }\ 64\ \xrightarrow{\ HBr\ }\qquad (C_6H_5)_3\overset{\ominus}{P}\!\!-\!\!C(CH_3)_2
$$

$$
O\!\!=\!\!C\!\!-\!\!C(C_6H_5)_2 \qquad\qquad\qquad\qquad\qquad\qquad O\!\!=\!\!CCH(C_6H_5)_2
$$

$$
CH_3
$$

whether **64** has the structure of a zwitterion or that of a four-membered
cyclic compound like **61**.

The final step C of the Wittig reaction, *cis* elimination of triphenyl-
phosphine oxide by way of the four-membered ring compound **61**, is
formally related to the decomposition of a phosphonium alkoxide into a
phosphine oxide and a hydrocarbon.[67]

$$
(C_6H_5)_3\overset{\ominus}{P}\!\!-\!\!\!-\!\!\!-\!\!C\!\!<\!\!{}^{R_1}_{R_2}
$$

$$
{}^{\ominus}O\!\!-\!\!\!-\!\!\!-\!\!C\!\!<\!\!{}^{R_3}_{R_4}\qquad \xrightarrow{\ B\ }
$$

$$
\mathbf{60}
$$

$$
(C_6H_5)_3P\!\!-\!\!\!-\!\!\!-\!\!C\!\!<\!\!{}^{R_1}_{R_2}
$$

$$
O\!\!-\!\!\!-\!\!\!-\!\!C\!\!<\!\!{}^{R_3}_{R_4}\qquad \xrightarrow{\ C\ }\ (C_6H_5)_3PO\ \div\ {}^{R_1}_{R_2}\!\!>\!\!C\!\!=\!\!C\!\!<\!\!{}^{R_3}_{R_4}
$$

$$
\mathbf{61}
$$

$$
(CH_3)_3\overset{\ominus}{P}\!\!-\!\!CH_3 \rightleftharpoons \quad (CH_3)_3P\!\!-\!\!\!-\!\!CH_3
$$

$$
{}^{\ominus}OC_2H_5 \qquad\qquad O\!\!-\!\!\!-\!\!C_2H_5 \quad \rightarrow\ (CH_3)_3PO\ \div\ C_3H_8
$$

Since it has never been observed that step C is the slowest and, therefore,
the rate-determining step in a Wittig reaction. it cannot be decided at the
present moment whether the four-membered ring compound **61** with a
pentavalent phosphorus atom is actually an intermediate or a transition
state. Depending on the reactants, however, either step A or B may
become rate-determining. Studies of the interaction of fluorenylidene

phosphoranes with a number of substituted carbonyl compounds showed that, with resonance-stabilized phosphoranes, the first step, formation of a betaine, is rate-determining.[29,49,50] Introduction of electron-with-drawing substituents into the benzaldehyde molecule resulted in an increased rate of reaction with fluorenylidenetriphenylphosphorane (11). The reverse was true with electron-releasing substituents. No reaction

	R_1 $C=O$ R_2	Yield, %
	$p\text{-}O_2NC_6H_4CHO$	96
	$p\text{-}ClC_6H_4CHO$	93
	C_6H_5CHO	84
	$p\text{-}CH_3OC_6H_4CHO$	37
	$p\text{-}(CH_3)_2NC_6H_4CHO$	0

was observed with ketones such as acetone, benzophenone, 4,4'-dinitro-benzophenone, and fluorenone, but 2,4,7-trinitrofluorenone and the phosphorane 11 gave the corresponding olefin in quantitative yield.

A characteristic feature of resonance-stabilized phosphoranes, for which addition of the ylide to the carbonyl group is the critical step, is that replacement of the phenyl groups by alkyl groups facilitates formation of olefins. This is the result of the fact that electron-releasing groups on phosphorus result in a larger contribution to the ground state of the more reactive ylide form. Replacement of the phenyl groups in 11 by n-butyl groups does, indeed, give rise to a considerably more reactive phosphorane,[29] which under otherwise equal conditions gives almost quanti-tative yields of olefins with all the benzaldehyde derivatives mentioned above. In addition, it will react with a number of ketones which are completely unreactive toward the triphenyl derivative 11. Thus good yields of olefins are obtained with 4,4'-dinitrobenzophenone as well as with m- and p-nitroacetophenone; the unsubstituted ketones will not react. Replacement of phenyl groups on phosphorus by alkyl groups such as methyl[58,151] or cyclohexyl[28] has a favorable effect on the yields of the Wittig reaction of other resonance-stabilized alkylidene phosphoranes

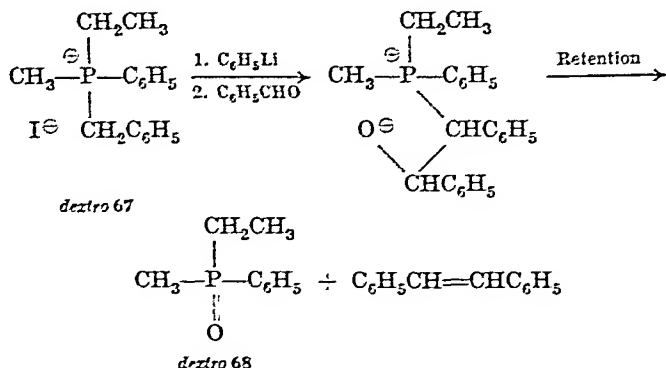[151] Trippett and Walker, *Chem. Ind. (London)*, 1960, 933.

as well.   In no case was it possible to isolate betaine intermediates such as 60 or 62.   Addition of hydrogen bromide gave only starting materials and end products,[29] a result which again supports the assumption that A is the slowest step, followed rapidly by steps B and C.

Recent kinetic studies with resonance-stabilized alkylidene phosphoranes indicate that the over-all reaction is best described as a slow, reversible formation of the betaine (rate-controlling) with rapid decomposition of the betaine into phosphine oxide and olefin.[152-154]

A completely different case is the interaction of carbonyl compounds with the reactive alkylidene phosphoranes, which constitute the majority of the Wittig reagents.[155]   Here the addition of the ylides to the carbonyl compounds takes place within a few minutes, whereas the subsequent decomposition of the betaines into phosphine oxide and olefins often requires prolonged standing at room temperature or heating for a number of hours.   Step B, decomposition of the betaine, is therefore rate-determining.   Consequently electron-releasing groups on phosphorus, despite their facilitation of step A, will impede the subsequent decomposition via the four-membered cyclic intermediate, since the phosphorus is less able to accept the anionic betaine oxygen.   Thus interaction of benzophenone with methylenetrimethylphosphorane led only to the betaine 65, which could be characterized as the hydroiodide,[102] whereas methylenetriphenylphosphorane[1] under the same conditions gave an almost quantitative yield of olefin.   Prolonged heating of the betaine 65 in tetrahydrofuran was

$$(CH_3)_3P{=}CH_2 + (C_6H_5)_2CO \longrightarrow (CH_3)_3\overset{\ominus}{P}{-}CH_2C(C_6H_5)_2 \overset{HI}{\longrightarrow}$$
$$\underset{O\,\ominus}{|}$$

<center>65</center>

$$(CH_3)_3\overset{\ominus}{P}{-}CH_2C(C_6H_5)_2$$
$$\underset{I\,\ominus\qquad OH}{|}$$

required in order to effect decomposition into trimethylphosphine oxide and 1,1-diphenylethylene, but even then the yield was less than 40%.[55,155]

A number of other methylene phosphoranes (66a–e) containing electron-releasing groups on phosphorus have also been investigated.[155]   In agreement with the assumption that electron-releasing groups on phosphorus

considerably decrease the activation energy for step A, it was observed that betaine formation was very rapid for each compound. The subsequent decomposition of the betaine by steps B and C, however, was more difficult in all examples and in some did not occur at all.

$(p\text{-}CH_3C_6H_4)_3P{=}CH_2$ $(p\text{-}CH_3OC_6H_4)_3P{=}CH_2$ $(o\text{-}CH_3OC_6H_4)_3P{=}CH_2$
66a   66b   66c

$$\left(\underset{N}{\bigcirc}\right)_3\!P{=}CH_2 \qquad \left(\underset{O}{\bigcirc}\right)_3\!P{=}CH_2$$
66d   66e

Since the polarity of the carbonyl group is of little consequence when the second step of the Wittig reaction is rate-determining, differently substituted aldehydes or ketones will usually give olefins in about the same yields. It is striking, furthermore, that the reactive phosphoranes, unlike the resonance-stabilized phosphoranes, react more readily with benzophenone than with benzaldehyde. Nucleophilic attack on benzaldehyde will in each case be easier than on the less reactive benzophenone and, consequently, reaction with the aldehyde will be preferred by the phosphoranes of low reactivity where the first step of the Wittig reaction requires the larger activation energy. However, introduction of phenyl groups on the β-carbon atom will facilitate the decomposition of the betaine into phosphine oxide and olefin (i.e., the rate-determining step with the reactive phosphoranes), and this will result in a more rapid collapse of the benzophenone adduct as compared with the benzaldehyde adduct. In general, it may be said that, whenever reaction of an ylide with benzophenone is faster than with benzaldehyde, the second step of the reaction, the decomposition of the betaine, is rate-determining. This explains why a number of resonance-stabilized alkylidene phosphoranes will react exclusively with aldehydes but not with benzophenone, whereas some of the reactive phosphoranes will interact readily with benzophenone but not with benzaldehyde. It also makes clear why betaines can usually be isolated only when benzaldehyde is used as the carbonyl component, whereas the benzophenone adducts as a rule are much less stable. Only from the methylene phosphoranes 66d and 66e was it possible to isolate adducts with benzophenone, since decomposition of the betaine is rendered extremely difficult as a consequence of the high electron density on phosphorus;[155] but even these adducts are less stable than the corresponding benzaldehyde adducts, which cannot be decomposed into olefin and phosphine oxide. The marked stability of the ketene adduct 64 is probably due to its stabilization by resonance.

Stereochemistry

Experiments with the optically active phosphonium salts **67** showed that the Wittig reaction takes place with retention of configuration on phosphorus.[156,157]

$$
\begin{array}{c}
\underset{\text{dextro 67}}{
\begin{array}{c}
\text{CH}_2\text{CH}_3 \\
| \\
\text{CH}_3\text{—}\overset{\ominus}{\text{P}}\text{—C}_6\text{H}_5 \\
| \\
\text{I}^{\ominus}\quad\text{CH}_2\text{C}_6\text{H}_5
\end{array}}
\quad\xrightarrow[\text{2. C}_6\text{H}_5\text{CHO}]{\text{1. C}_6\text{H}_5\text{Li}}\quad
\begin{array}{c}
\text{CH}_2\text{CH}_3 \\
| \\
\text{CH}_3\text{—}\overset{\ominus}{\text{P}}\text{—C}_6\text{H}_5 \\
\underset{\text{CHC}_6\text{H}_5}{\overset{\diagup\quad\diagdown\text{CHC}_6\text{H}_5}{\text{O}^{\ominus}}}
\end{array}
\quad\xrightarrow{\text{Retention}}
\end{array}
$$

$$
\underset{\text{dextro 68}}{
\begin{array}{c}
\text{CH}_2\text{CH}_3 \\
| \\
\text{CH}_3\text{—P—C}_6\text{H}_5 \\
\| \\
\text{O}
\end{array}}
\;\div\; \text{C}_6\text{H}_5\text{CH}\text{=}\text{CHC}_6\text{H}_5
$$

The same phosphine oxide, *dextro* **68**, is formed with inversion from the phosphonium salt, *levo* **67**, under the influence of alkali.

$$
\begin{array}{ccc}
\textit{dextro}\text{ salt} & \xrightarrow[\text{(Inversion)}]{\text{OH}^{\ominus}} & \textit{levo}\text{ oxide} \\
\Big\downarrow{\small\begin{array}{c}\text{Wittig}\\(\text{Retention})\end{array}} & & \Big\uparrow{\small\begin{array}{c}\text{Wittig}\\(\text{Retention})\end{array}} \\
\textit{dextro}\text{ oxide} & \xleftarrow[\text{(Inversion)}]{\text{OH}^{\ominus}} & \textit{levo}\text{ salt}
\end{array}
$$
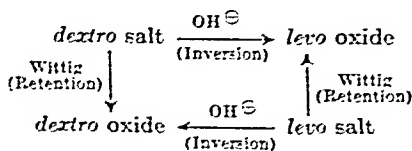
If the ylide and carbonyl components are unsymmetrically substituted, a mixture of *cis* and *trans* olefins is usually obtained. As a rule, the *trans* olefin predominates, as illustrated by the reaction of benzylidene-triphenylphosphorane with benzaldehyde which leads to a mixture containing 70% *trans-* and 30% *cis-*stilbene.[2] However, exclusive

$$
(\text{C}_6\text{H}_5)_3\text{P}\text{=}\text{CHC}_6\text{H}_5 \;\div\; \text{C}_6\text{H}_5\text{CHO} \longrightarrow
\begin{array}{c}
\text{H}\qquad\text{C}_6\text{H}_5 \\
\diagdown\!\!\diagup \\
\diagup\!\!\diagdown \\
\text{C}_6\text{H}_5\qquad\text{H} \\
(70\%)
\end{array}
\;\div\;
\begin{array}{c}
\text{C}_6\text{H}_5\qquad\text{C}_6\text{H}_5 \\
\diagdown\!\!\diagup \\
\diagup\!\!\diagdown \\
\text{H}\qquad\text{H} \\
(30\%)
\end{array}
$$
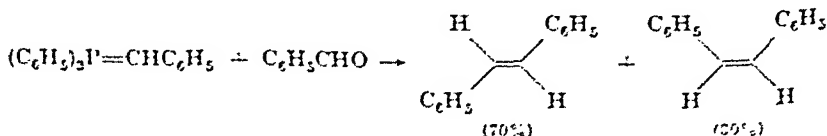
predominance of the *cis* isomer.[159-161] Strikingly, the *trans* isomer is always formed predominantly or exclusively if resonance-stabilized alkylidene phosphoranes are used. Thus almost pure *trans* olefins were obtained by using cyanomethylenetriphenylphosphorane[42,43] and carbomethoxymethylenetriphenylphosphorane[39,162,163] as well as their derivatives.[40,111,117,164] The observation that carbomethoxyethylidenetriphenylphosphorane (69) gives the pure *trans* compound with acrolein led to the systematic investigation of this reaction.[164]

$$(C_6H_5)_3P=CCO_2CH_3 + CH_2=CHCHO \rightarrow CH_2=CHCH$$
$$\underset{CH_3}{\underset{|}{}} \qquad\qquad\qquad CH_3CCO_2CH_3$$
$$\underset{69}{}$$
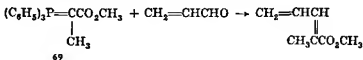
By means of the Wittig reaction, methyl 2-methyl-2-butenoate was prepared in two different ways. The ylide 69 and acetaldehyde furnished almost exclusively methyl tiglate (71), i.e., the *trans* isomer. Methyl pyruvate and ethylidenetriphenylphosphorane gave a mixture of isomers that contained 32% of the *cis* compound, methyl angelate (73).[164] In

$$CH_3CHO + (C_6H_5)_3P=C(CH_3)CO_2CH_3$$
$$\underset{69}{}$$
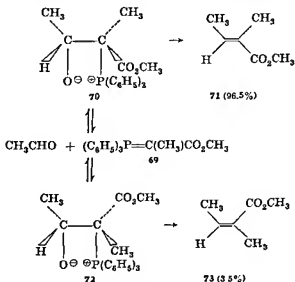
159 Wailes, *Chem. Ind.* (*London*), 1958, 1086.
160 Bohlmann, Inhoffen, and Herbst, *Chem. Ber.*, 90, 1661 (1957).
161 Truscheit and Eiter, *Ann.*, 658, 65 (1962).
162 Novikov and Shvekhgeimer, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.*, 1960, 673 [*C.A.*, 54, 22474h (1960)].
163 Kucherov, Kovalev, Kogan, and Yanovskaya, *Dokl. Akad. Nauk SSSR*, 138, 1115 (1961) [*C.A.*, 55, 24560i (1961)].
164 House and Rasmusson, *J. Org. Chem.*, 26, 4278 (1961).

$$
\underset{\mathbf{74}}{\underset{\substack{\text{H} \quad\quad\quad \text{CO}_2\text{CH}_3 \\ (\text{C}_6\text{H}_5)_3\text{P}^{\ominus} \ ^{\ominus}\text{O}}}{\overset{\text{CH}_3 \quad\quad \text{CH}_3}{\text{C}\!-\!\text{C}}}} \rightarrow \underset{\mathbf{71\ (68\%)}}{\underset{\text{H} \quad\quad\quad \text{CO}_2\text{CH}_3}{\overset{\text{CH}_3 \quad \text{CH}_3}{\text{C}\!=\!\text{C}}}}
$$

$$
\uparrow
$$

$$
\text{CH}_3\text{COCO}_2\text{CH}_3 + (\text{C}_6\text{H}_5)_3\text{P}\!=\!\text{CHCH}_3
$$

$$
\downarrow
$$

$$
\underset{\mathbf{75}}{\underset{\substack{\text{H} \quad\quad\quad\quad \text{CH}_3 \\ (\text{C}_6\text{H}_5)_3\text{P}^{\ominus} \ ^{\ominus}\text{O}}}{\overset{\text{CH}_3 \quad\quad \text{CO}_2\text{CH}_3}{\text{C}\!-\!\text{C}}}} \rightarrow \underset{\mathbf{73\ (32\%)}}{\underset{\text{H} \quad\quad\quad \text{CH}_3}{\overset{\text{CH}_3 \quad \text{CO}_2\text{CH}_3}{\text{C}\!=\!\text{C}}}}
$$
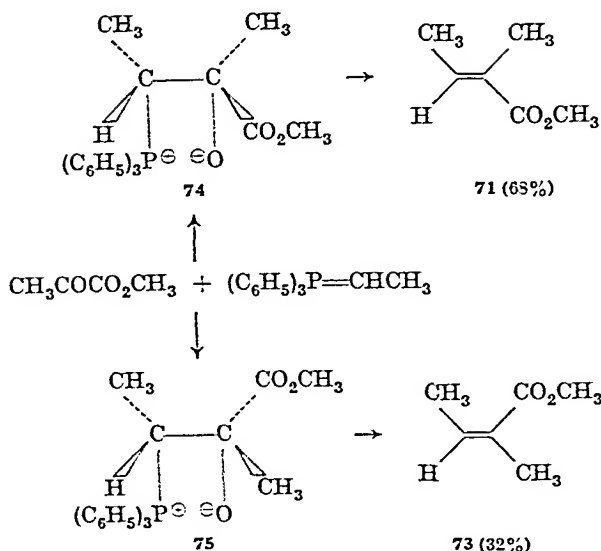
order to rationalize the observed isomer distributions, one may assume that the resonance-stabilized phosphorane 69 is in equilibrium with the two betaines 70 and 72. Here the first and, for the unreactive phosphoranes, slowest step will probably be reversible, so that the reaction may proceed predominantly by way of the sterically less hindered betaine 70, thus leading to the *trans* olefin. While such an interpretation of the isomer distribution from the stabilized ylide 69 seems reasonably satisfactory, the products formed from the reactive ethylidenephosphorane are harder to rationalize. Decomposition of the betaines derived from reactive phosphoranes to starting materials was originally thought not to occur.[155] More recent studies, however, provide convincing evidence that benzaldehyde is formed from a simple betaine under mild conditions.[165]

$$
\underset{\substack{| \\ ^{\ominus}\text{O}\!-\!\text{CHC}_6\text{H}_5}}{\overset{\overset{\frown}{\ominus}}{(\text{C}_6\text{H}_5)_3\text{P}\!-\!\text{CH}_2}} \rightleftharpoons (\text{C}_6\text{H}_5)_3\text{P}\!=\!\text{CH}_2 + \underset{\substack{| \\ \text{H}}}{\text{O}\!=\!\text{CC}_6\text{H}_5}
$$
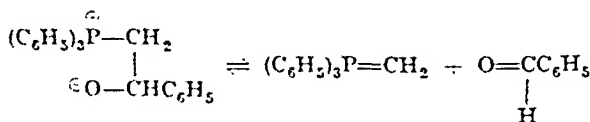
Thus it seems that a full understanding of the isomer distributions outlined above must await further research.

Another example of the differences in isomer distributions in the Wittig reaction is the preparation of 4-nitro-4'-methoxystilbene (78) by two

[155] Fivász, Hudson, and Salvadori, *Helv. Chim. Acta*, 46, 1560 (1963).

methods.[166] Reaction of the resonance-stabilized *p*-nitrobenzylidene-
phosphorane (76) with the relatively unreactive anisaldehyde leads to the

$$(C_6H_5)_3P=CHC_6H_4NO_2\text{-}p + p\text{-}CH_3OC_6H_4CHO$$
$$\underset{76}{}$$

$$\downarrow 89\% \text{ } trans \text{ only}$$

$$p\text{-}CH_3OC_6H_4CH=CHC_6H_4NO_2\text{-}p$$
$$\underset{78}{}$$

$$\uparrow 89\% \text{ } cis \text{ and } trans \text{ (1:1)}$$

$$(C_6H_5)_3P=CHC_6H_4OCH_3\text{-}p + p\text{-}O_2NC_6H_4CHO$$
$$\underset{77}{}$$
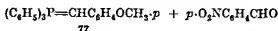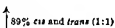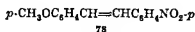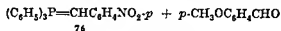
exclusive formation of the *trans* compound 78. The less stable, more
reactive *p*-methoxybenzylidenephosphorane (77), on the other hand,
reacts with the extremely reactive *p*-nitrobenzaldehyde to give a mixture
of the *cis*- and *trans*-stilbenes 78 in the ratio of 1:1.

In the reactions of resonance-stabilized alkylidene phosphoranes with
carbonyl compounds, the isomer ratio may be shifted further in favor of
the *trans* products if the stability of the initially formed betaines 79a and
79b is increased, thus preventing further reaction before equilibrium has
been reached. This was accomplished by substituting cyclohexyl groups
for the phenyl groups on phosphorus.[28] The phosphorus is thus rendered
less electrophilic, and the conversion of 79 to the end products by way of
the four-membered ring compound 80 becomes more difficult. If the rate
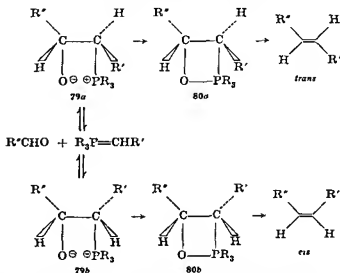
[166] Ketcham, Jambotkar, and Martinelli, *J. Org. Chem.*, 27, 4666 (1962).

of conversion of **79** to **80** is so rapid that the equilibrium $79a \rightleftharpoons 79b$ cannot be established, considerable amounts of *cis* olefins will be formed in addition to the *trans* compounds. If, on the other hand, establishment of the equilibrium is possible, the betaine **79a** leading to the *trans* isomer will be energetically favored to a large extent.

An effort to account for the predominance of *trans* compounds from resonance-stabilized phosphoranes has been made by postulating a nucleophilic attack on the phosphorus atom by the oxygen of the carbonyl component as the first step in such reactions.[114] Other studies, however, indicate that the primary step is probably nucleophilic attack by the ylide carbon atom on the carbonyl carbon atom.[167,168] In addition, substitution of phenyl groups on the phosphorus atom by cyclohexyl groups[28] leads not only to an increased yield of *trans* olefins but also to an increase of the total yield. Electron-releasing groups on phosphorus would be expected to impede rather than to facilitate the nucleophilic attack of the carbonyl oxygen on the phosphorus atom.

Studies have also been reported which indicate that reactive phosphoranes with aldehydes tend to give increased amounts of *cis* isomers in the products when the reaction is carried out in the presence of Lewis bases.[114,169–172]

SCOPE AND LIMITATIONS

In the few years since the discovery of the Wittig reaction, many olefins have been synthesized by this method. The reaction is not limited to simple alkyl- or aryl-substituted ethylene derivatives but is also applicable to the synthesis of α,β-unsaturated carbonyl compounds and carboxylic esters as well as vinyl halides and vinyl ethers. The large number of natural products prepared by the Wittig reaction speaks for the importance that this olefin synthesis has attained in a short period.

Alkyl-Substituted Olefins

The Wittig reaction is especially valuable for the introduction of exocyclic double bonds and is the only method for converting a cyclic

[167] Goetz, Nerdel, and Michaelis, *Naturwiss.*, **14**, 496 (1963).

[168] Speziale and Ratts, *J. Org. Chem.*, **28**, 465 (1963).

[169] Bergel'son, Vaver, Barsukov, and Shemyakin, *Dokl. Akad. Nauk SSSR*, **143**, 111 (1962) [*C.A.*, **57**, 7298e (1962)].

[170] Bergel'son, Vaver, Kovtun, Senyavina, and Shemyakin, *Zh. Obshch. Khim.*, **32**, 1802 (1962) [*C.A.*, **58**, 4415z (1963)].

[171] Bergel'son, Vaver, and Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1960, 1960 [*C.A.*, **55**, 14294e (1961)].

[172] Bergel'son, Vaver, and Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1961, 729 [*C.A.*, **55**, 22196e (1961)].

ketone to the corresponding exocyclic olefin. The Grignard method is well known to give practically only the endocyclic isomer (Saytzeff rule). For example, cyclohexanone and methylenetriphenylphosphorane give methylenecyclohexane.[2]

$$\bigcirc=O + (C_6H_5)_3P=CH_2 \rightarrow \bigcirc=CH_2$$
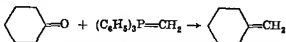
Similarly a whole series of methylenesteroids has been synthesized, and a methylene group has been successfully introduced into the vitamin D_2 skeleton. Recently methylenecycloheptane and methylenecyclooctane have been prepared by this method,[173] as were derivatives of methylenedihydronaphthalene and methylenetetralin.[174] 1-Methylene-2,2-dimethyltetralin (81), for instance, was obtained in 83% yield.
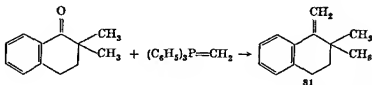
Catalytic hydrogenation of the methylene compounds permits the conversion $>C=O \rightarrow >CHCH_3$.[175-177]

The synthesis of 1,2-disubstituted ethylene derivatives from aldehydes and monosubstituted methylene triphenylphosphoranes can be effected in two ways.

$$RCHO + (C_6H_5)_3P=CHR'$$
$$\searrow$$
$$RCH=CHR'$$
$$\nearrow$$
$$R'CHO + (C_6H_5)_3P=CHR$$
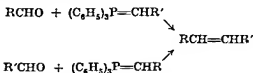
As a rule, mixtures of cis and trans olefins are formed in these reactions, for instance, in the synthesis of 1,1,1-triphenyl-3-pentene (82) from β,β,β-triphenylpropionaldehyde and ethylidenetriphenylphosphorane.[178]

$$(C_6H_5)_3CCH_2CHO + (C_6H_5)_3P=CHCH_3 \xrightarrow{53\%} (C_6H_5)_3CCH_2CH=CHCH_3$$
$$82$$

Unsaturated aldehydes can also be used. Propargylaldehyde, for instance, reacts with n-dodecylidenetriphenylphosphorane to give pentadec-3-en-1-yne (83).[159] The strikingly large amount of cis compound

[173] Schiesheim, Müller, and Rowe, J. Am Chem. Soc., 84, 3164 (1962).
[174] Wittig, Heppe, and Eicher, Ann., 643, 47 (1961).
[175] Chadha and Rapoport, J. Am. Chem. Soc., 79, 5730 (1957).
[176] Buchi and MacLeod, J. Am. Chem. Soc., 84, 3205 (1962).
[177] DeGraw and Bonner, Tetrahedron, 18, 1311 (1962).
[178] Wittig and Wittenberg, Ann., 606, 1 (1957).

(80%) in the isomer mixture 83 is probably due to the presence of lithium bromide in the solution.

$$HC{\equiv}CCHO + (C_6H_5)_3P{=}CHC_{11}H_{23}\text{-}n \rightarrow HC{\equiv}CCH{=}CHC_{11}H_{23}\text{-}n$$
$$83$$
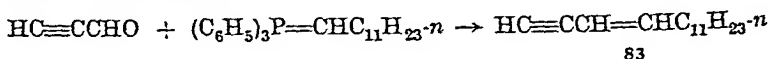
Both groups, R and R', may be unsaturated, as illustrated by the synthesis of hexa-3,5-dien-1-yne (84) from propargylaldehyde and allylidenetriphenylphosphorane.[179]

$$HC{\equiv}CCHO + (C_6H_5)_3P{=}CHCH{=}CH_2 \rightarrow HC{\equiv}CCH{=}CHCH{=}CH_2$$
$$84$$
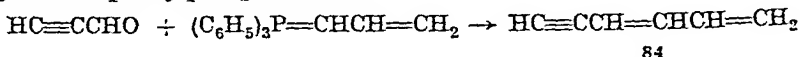
A series of compounds containing alternating double and triple bonds was synthesized in this way;[180] for instance, the C_{20} hydrocarbon containing alternating pairs of ethylenic and acetylenic linkages.

$$(CH_3)_3C(C{\equiv}C)_2CHO + (C_6H_5)_3P{=}CHCH{=}CH(C{\equiv}C)_2C(CH_3)_3 \xrightarrow{19\%}$$
$$(CH_3)_3C(C{\equiv}C)_2(CH{=}CH)_2(C{\equiv}C)_2C(CH_3)_3$$
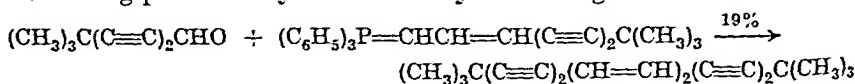
The interaction of bifunctional carbonyl compounds with 2 equivalents of phosphorane can also be used for the preparation of polyenes, as shown in the synthesis of the dimethylpolyene 85.[181]

$$OCHCH{=}CH(C{\equiv}C)_2CH{=}CHCHO + 2(C_6H_5)_3P{=}CH(CH{=}CH)_2CH_3 \rightarrow$$
$$CH_3(CH{=}CH)_4(C{\equiv}C)_2(CH{=}CH)_4CH_3 \xrightarrow{H_2} CH_3(CH{=}CH)_{10}CH_3$$
$$85$$
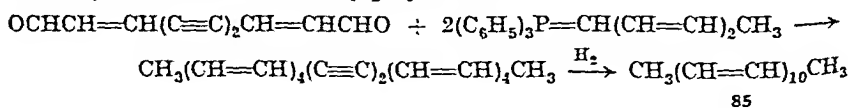
This method has proved especially valuable in the synthesis of carotenoids. Conversely, bifunctional phosphoranes can be used. Thus β-carotene (88) was prepared from β-ionylideneacetaldehyde (86) and the bis-ylide 87.[80]
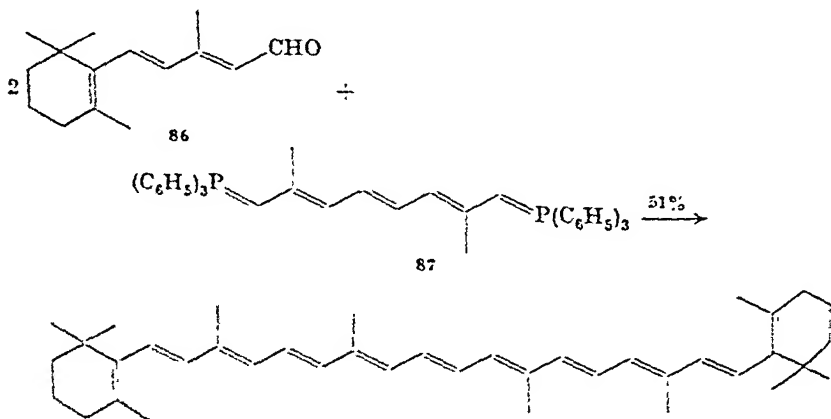
[179] Bohlmann and Inhoffen, Chem. Ber., 89, 21 (1956).
[180] Bohlmann and Politt, Chem. Ber., 90, 130 (1957).
[181] Bohlmann and Mannhardt, Chem. Ber., 89, 1307 (1956).

Tritium-labeled olefins have been prepared by the action of tritium-labeled alkylidene phosphoranes with aldehydes.[68]

$$RCHO + (C_6H_5)_3P=CTR' \rightarrow RCH=CTR'$$
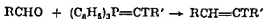
1,1,2-Trisubstituted ethylene derivatives may be prepared by two different paths.
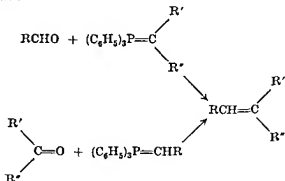
By using the first path, 1,1,1-triphenyl-4-methyl-3-pentene (89) was obtained in 68% yield starting from β,β,β-triphenylpropionaldehyde.[178]

$$(C_6H_5)_3CCH_2CHO + (C_6H_5)_3P=C(CH_3)_2 \rightarrow (C_6H_5)_3CCH_2CH=C(CH_3)_2$$
$$\text{89}$$
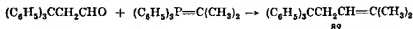
An illustration of the second method, which starts from ketones, is the preparation of a number of dimethylheptadienes (geraniolenes) and methylhexenes such as 2-methyl-2-hexene (90) from acetone and n-butylidenetriphenylphosphorane.[182] This method has been applied most

$$(CH_3)_2C=O + (C_6H_5)_3P=CHC_3H_7\text{-}n \xrightarrow{20\%} (CH_3)_2C=CHC_3H_7\text{-}n$$
$$\text{90}$$
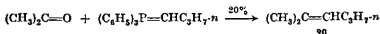
frequently in the area of natural products chemistry. Bifunctional carbonyl compounds or bifunctional ylides (squalene synthesis) have been used for this purpose.

Starting from cyclic ketones, the corresponding exocyclic olefins are obtained, as shown by the preparation of dicyclohexylideneethane (91) from cyclohexanone.[183,184]
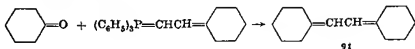
[182] Ansell and Thomas, J. Chem. Soc., 1961, 539.

[183] Harrison, Lythgoe, and Trippett, J. Chem. Soc., 1955, 4016

[184] Harrison, Lythgoe, and Trippett, Chem. Ind. (London), 1955, 507.

Substituted cyclohexanes have been prepared by variation of either the carbonyl[158,183,184] or the ylide component.[69] In the first case the *trans*
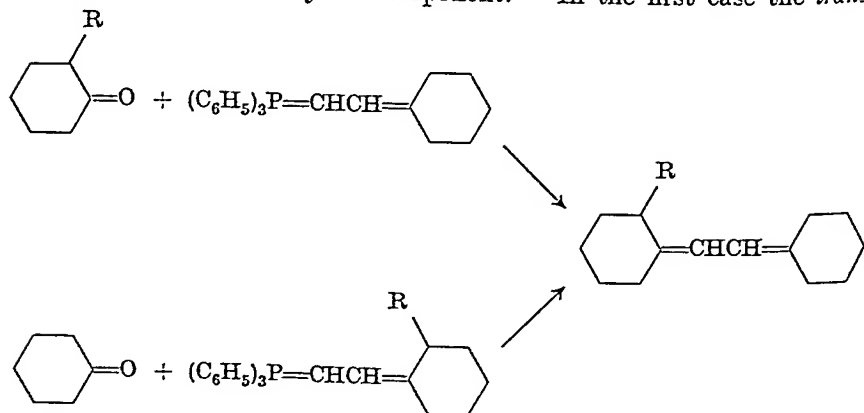
compound, $R = CH_2N(CH_3)_2$, was obtained exclusively. In the second case, starting from the *cis* ylide, the *cis* compound, $R = CH_2OH$ or OH, was obtained predominantly; increasing the reaction temperature resulted in increased formation of the *trans* olefin. When the substituent R was Br, subsequent elimination of hydrogen bromide under the influence of the ylide was observed. The triene so obtained did not contain any exocyclic double bonds.[16]
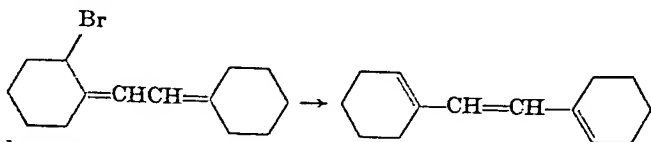
With benzylidenetriphenylphosphorane, cyclohexanone gives benzylidenecyclohexane in 60% yield.[3] The same compound is obtained in 70% yield from the deep red cyclohexylidenetriphenylphosphorane and benzaldehyde.[155]
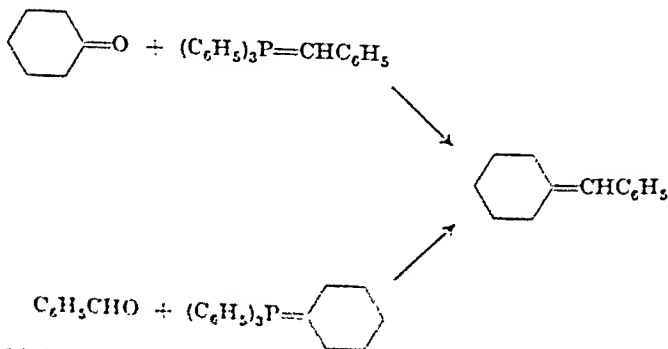
[155] U. Schöllkopf, Doctoral Dissertation, Universität Tübingen, 1956.

Cyclopentylidenetriphenylphosphorane, another ylide containing an exocyclic double bond, is also intensely colored. It reacts with benzaldehyde to give benzylidenecyclopentane.[185]

$$C_6H_5CHO + (C_6H_5)_3P = \text{(cyclopentyl)} \xrightarrow{85\%} C_6H_5CH = \text{(cyclopentyl)}$$
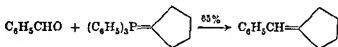
Aryl-Substituted Olefins

Styrene, the simplest monoaryl derivative of ethylene, has been obtained in 67% yield in the reaction of benzaldehyde with methylenetriphenylphosphorane.[2]

$$C_6H_5CHO + (C_6H_5)_3P = CH_2 \rightarrow C_6H_5CH = CH_2$$

Similarly, 9-vinylanthracene is obtained from 9-anthraldehyde.[186]
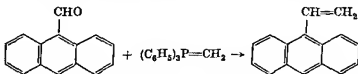
Vinyl aromatics are also accessible starting from the corresponding arylidene phosphoranes and formaldehyde,[187] as illustrated by the preparation of 4,4'-divinylbiphenyl in 80% yield. This route is especially

$$2CH_2O + (C_6H_5)_3P = CH \text{—⟨biphenyl⟩—} CH = P(C_6H_5)_3 \rightarrow$$

$$CH_2 = CH \text{—⟨biphenyl⟩—} CH = CH_2$$
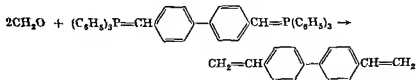
useful when the aromatic halogen compound is more accessible than the carbonyl compound. Aliphatic vinyl compounds may be prepared in a similar fashion.[188,189]

From o-phthalaldehyde and methylenetriphenylphosphorane, o-divinylbenzene is formed in 75% yield.[52]
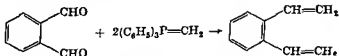
[185] Hawkins, *J. Chem. Soc.*, **1957**, 3858.

[186] Drefahl, Plotner, and Rudolph, *Chem. Ber.*, **93**, 998 (1960).

[187] Hauser, Miles, and Butler, 142nd Meeting, Am. Chem. Soc., Atlantic City, N J, Sept., 1962, Abstracts, p. 59Q.

[188] Hauser, Brooks, Miles, Raymond, and Butler, *J. Org. Chem.*, **28**, 372 (1963).

Starting from the bifunctional ylides **92** and **94**, 1,2-benzocyclohepta-1,3,6-triene (**93**) and 1,2-benzocycloöcta-1,3,7-triene (**95**), respectively, are obtained.[52]
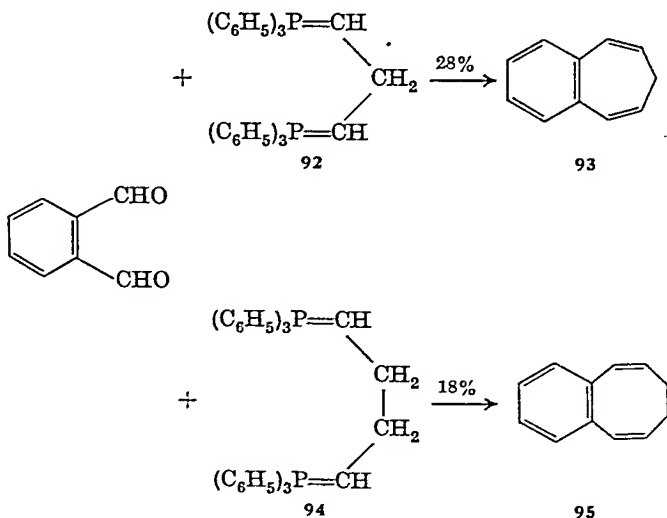
3-Benzoxepin (**96**) was prepared in an analogous manner.[190]
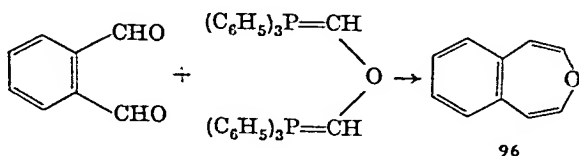
1,1-Diaryl olefins are particularly easy to obtain by the interaction of methylenetriphenylphosphorane and aromatic ketones.[1] Benzophenone
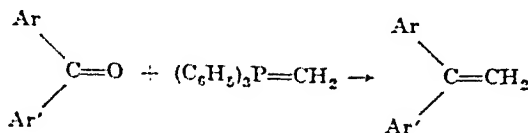
gave 1,1-diphenylethylene in 84% yield.[1] For preparative purposes, however, the Wittig reaction with aromatic ketones is of minor importance

190 Dimroth and Pohl, *Angew. Chem.*, **73**, 436 (1961).

because aromatic ketones can usually be converted to the corresponding olefins without difficulty by the Grignard method, since an isomerization of the double bond cannot take place. There are reactions, however, in which the Grignard method fails to give the desired product. Thus the reaction of 2,2'-dibenzoylbiphenyl (97) with methyllithium followed by hydrolysis and dehydration gives the cyclic hydrocarbon 99 rather than 2,2'-distyrylbiphenyl (98), whereas the latter can be prepared in 85% yield by the Wittig reaction.[191]
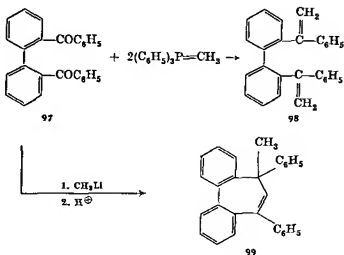
The preparation of olefins from nitro-substituted carbonyl compounds is not possible by the Grignard method because the reagent attacks nitro groups. This complication can usually be avoided by using an alkylidene phosphorane as in the accompanying example.[2]
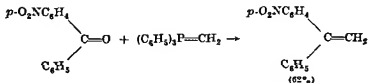
Only extremely nucleophilic alkylidene phosphoranes containing electron-releasing groups on phosphorus, such as 100, attack nitro groups. The ylide 100 has been reported to react with nitrobenzophenone to give

191 Wittig and Stilz, *Ann.*, 598, 93 (1956).

dark-colored products; olefin formation could not be observed.[192] Normally, however, olefins are formed very readily from nitro ketones and nitro aldehydes, and yields of over 90 % are not unusual.[3,29,49,50,166,193]

$$p\text{-}(CH_3)_2NC_6H_4 - \overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{P}} = CH_2$$

100
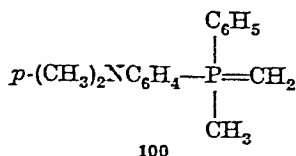
1,2-Diaryl olefins or stilbenes are formed in the interaction of aromatic aldehydes with aryl-substituted methylene triphenylphosphoranes. Mixtures of *cis* and *trans* olefins are obtained, the ratio in this synthesis of

$$ArCHO + (C_6H_5)_3P = CHAr' \searrow$$
$$ArCH = CHAr'$$
$$Ar'CHO + (C_6H_5)_3P = CHAr \nearrow$$

$$C_6H_5CHO + (C_6H_5)_3P = CHC_6H_5 \rightarrow C_6H_5CH = CHC_6H_5$$
(82%)
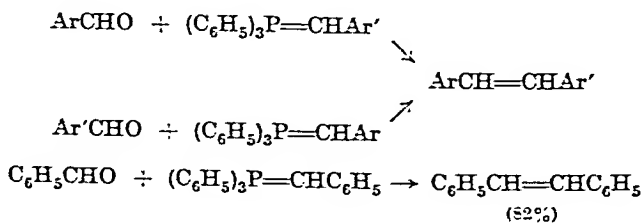
stilbene being 70% *trans* and 30% *cis*.[2] By using the alkoxide method, the ratio was found to be 47:53, the increased amount of the *cis* isomer being ascribed to increased polarity of the solvent.[3] The different isomer ratios obtained in the synthesis of 4-nitro-4'-methoxystilbene by two different ways (Ar and Ar' exchanged) have been mentioned previously (p. 314).[166]

Reaction of 2-methoxy-3-methylbenzaldehyde with benzylidene-triphenylphosphorane gives 2-methoxy-3-methylstilbene.[194] A large
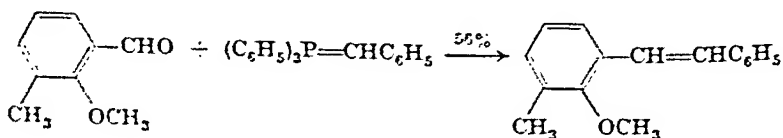
number of other stilbene derivatives has been prepared in a similar manner. The alkoxide method proved to be particularly useful for this

The preparation of symmetrical and unsymmetrical 1,2-diarylethylenes containing larger aromatic groups has also been reported.[197] 1,2-Bis-(3-pyrenyl)ethylene (101) is formed in 91 % yield.

101
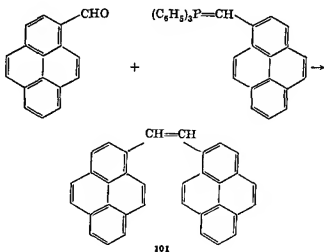
Stilbazole derivatives can be prepared from pyridine aldehydes.[198]

(56%)
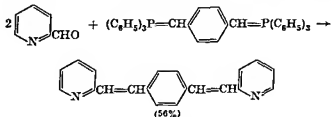
Distyrylbenzenes can be prepared similarly.[66,193]

$$2C_6H_5CHO + (C_6H_5)_3P=CH-\boxed{\quad}-CH=P(C_6H_5)_3 \rightarrow$$

$$C_6H_5CH=CH-\boxed{\quad}-CH=CHC_6H_5$$

(88%)
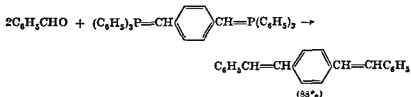
[197] Geerts and Martin, *Bull. Soc. Chim. Belges*, 69, 563 (1960) [*C.A.*, 55, 14410c (1961)].
[198] Drefahl, Plötner, and Buchner, *Chem. Ber.*, 94, 1824 (1961).

These compounds, which are of commercial interest as fluorescent brightening agents, can also be synthesized from terephthalaldehyde.[66,193,199–201]

$$p\text{-}OHCC_6H_4CHO \ + \ 2(C_6H_5)_3P\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CO_2CH_3 \ \rightarrow$$

$$CH_3O_2C\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CO_2CH_3$$

(73%)
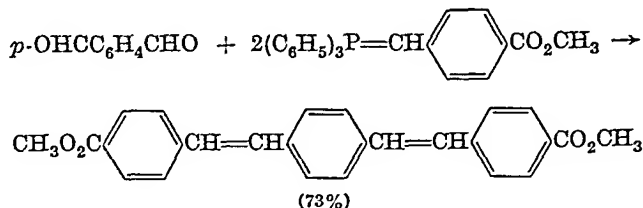
Longer chains with alternating benzene rings and ethylene groups can be prepared from stilbenedialdehyde.[196]

$$OHC\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CHO \ + \ 2(C_6H_5)_3P\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle \ \rightarrow$$

$$C_6H_5CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CH\!\!\left\langle\bigcirc\right\rangle\!\!CH\!\!=\!\!CHC_6H_5$$

(53%)
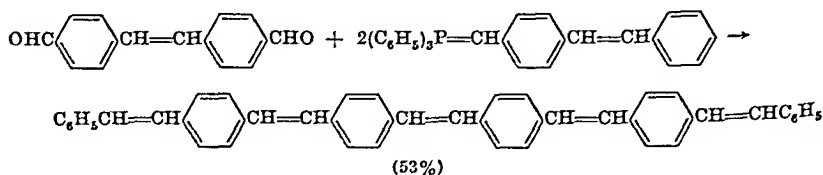
1,3-Distyrylbenzenes[66] and 1,2-distyrylbenzenes[201a] have also been synthesized. Starting from the 1,2-distyrylbenzene 102, the macrocyclic compound 103 can be prepared.[201a]

102
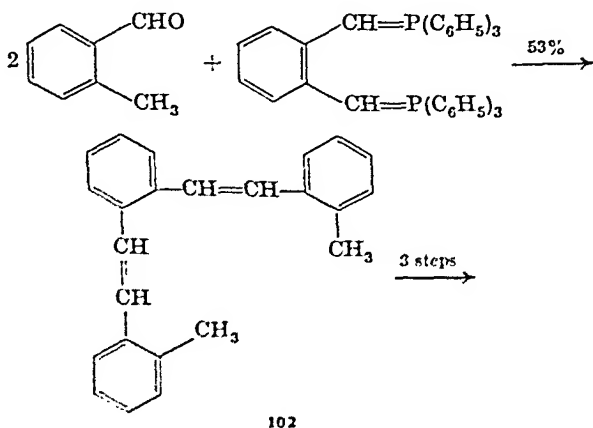
[199] Stilz, Pommer, Wolff, and Fessmann, Fr. pat. 1,266,088 (to BASF), 1959.
[193] Stilz, Pommer, Gehm, Schmidt, Mertens, Hehl, and Grunwald, Belg. pat. 599,724 (to BASF), 1959.
[201] Pommer, Sickel, Schwen, and Stilz, Belg. pat. 593,216 (to BASF), 1960.
[201a] Griffin, Martin, and Douglas, J. Org. Chem., 27, 1627 (1962).

103
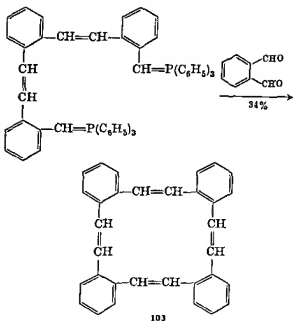
Cyclic compounds may also be prepared by intramolecular Wittig reactions. Thus the alkylidene phosphorane 104, which contains a carbonyl group, cyclizes to 1-phenylcyclopentene.[202]
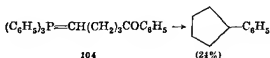
2-Benzoylethylidenetriphenylphosphorane (105), on the other hand, does not react intramolecularly to give 1-phenylcyclopropene. Instead an intermolecular condensation of two molecules of the phosphorane leads to 1,4-diphenyl-1,4-cyclohexadiene.[203]
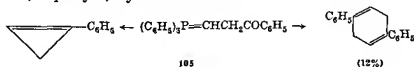
Aromatic compounds may also be prepared by using intramolecular Wittig reactions. The vinylog of benzoylmethylenetriphenylphosphorane

[202] Bieber and Eisman, *J. Org. Chem.*, **27**, 678 (1962).
[203] Griffin and Witschard, *J. Org. Chem.*, **27**, 3334 (1962).

107, prepared from the pyrylium salt **106,** cyclizes to symmetrical triphenylbenzene.[204]
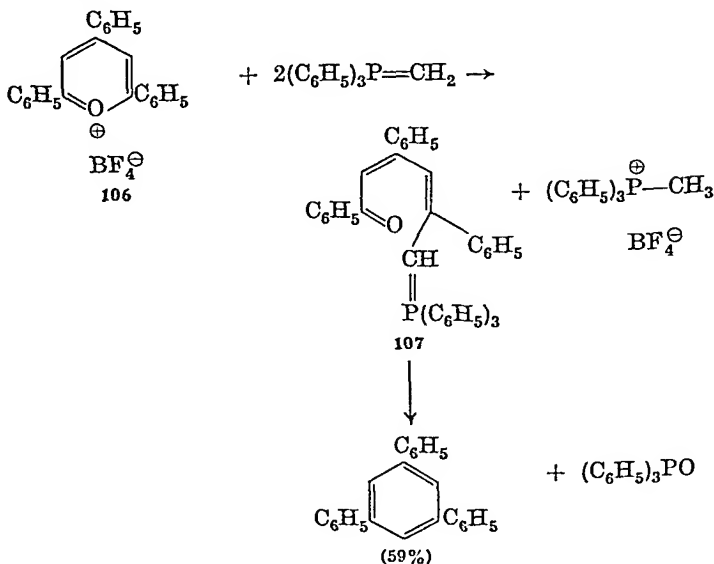
Cyclizations may also occur in the ylide prior to condensation with a carbonyl component.[205]
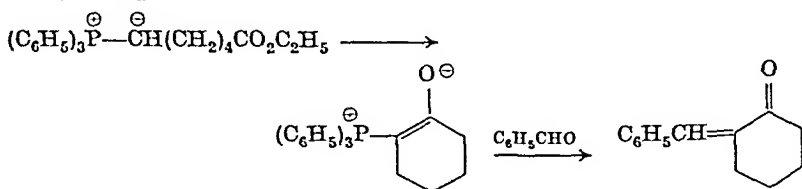
A cyclization has also been reported in which a rearrangement occurred in the alkylidene group of the phosphorane.[206]
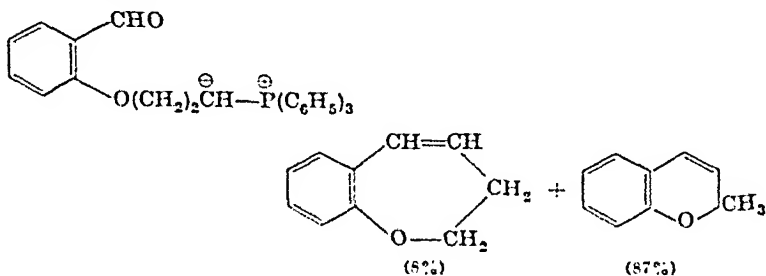
If there is no possibility for intramolecular ring closure, an intermolecular reaction may take place exclusively. p-Formylbenzylidenetriphenylphosphorane (108), for instance, polymerizes spontaneously to give a lemon-yellow compound 109 which melts above 360°.[207]

$$(C_6H_5)_3P{=}CH{-}\hspace{-2pt}\bigcirc\hspace{-2pt}{-}CHO \rightarrow OHC{-}\left[\bigcirc{-}CH{=}CH{-}\right]{-}\bigcirc{-}CHO$$

108   **109** (n=11)
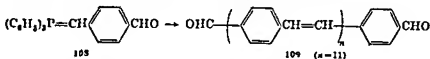
In a similar fashion, the colorless poly-m-xylylidene derivative 111, m.p. 180°, is obtained from the ylide 110.[208]

$$(C_6H_5)_3P{=}CH{-}\bigcirc\begin{matrix}CHO\\OCH_3\end{matrix}\rightarrow$$

110

$$OHC{-}\bigcirc\begin{matrix}\\OCH_3\end{matrix}{-}\left[CH{=}CH{-}\bigcirc\begin{matrix}\\OCH_3\end{matrix}\right]_n{-}\bigcirc{-}CHO$$

111
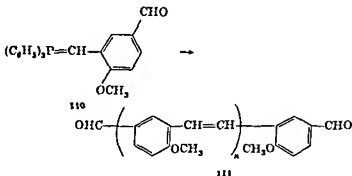
Polymerizations also can be effected by interaction of bifunctional carbonyl compounds with bis-ylides. Terephthalaldehyde reacts quantitatively with the bifunctional phosphorane 112 to give a yellow poly-p-xylylidene which, except for its degree of polymerization, is probably identical with the product 109 mentioned above.[208]

$$OHC{-}\bigcirc{-}CHO + (C_6H_5)_3P{=}CH{-}\bigcirc{-}CH{=}P(C_6H_5)_3 \rightarrow 109$$

112   (n=9)
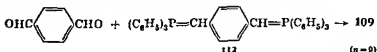
By means of the Wittig reaction, a large number of aryl-substituted butadiene derivatives and polyenes have been prepared. 1-Phenylbutadiene was obtained in two different ways.[2] Starting from cinnamaldehyde

$$C_6H_5CH{=}CHCHO + (C_6H_5)_3P{=}CH_2$$

A

B

$$C_6H_5CH{=}CHCH{=}CH_2$$

$$C_6H_5CHO + (C_6H_5)_3P{=}CHCH{=}CH_2$$
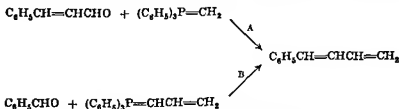
[207] A. Haag, Doctoral Dissertation, Universität Heidelberg, 1962.

[208] McDonald and Campbell, J. Am. Chem. Soc., 82, 4669 (1960).

(path A), no isomerization of the double bond took place and the *trans* isomer was obtained exclusively in 69% yield. Path B, on the other hand, gave 58% of a mixture containing 55% *trans*- and 45% *cis*-phenylbutadiene.
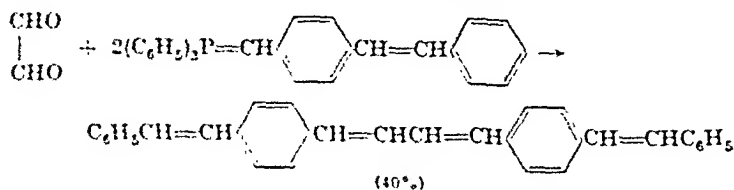
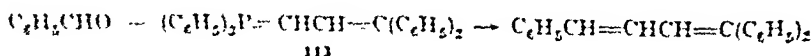1,1-Diphenylbutadiene was prepared from β-phenylcinnamaldehyde by using path A.[138]

$$(C_6H_5)_2C{=\!\!=}CHCHO \div (C_6H_5)_3P{=\!\!=}CH_2 \rightarrow (C_6H_5)_2C{=\!\!=}CHCH{=\!\!=}CH_2$$
$$(54\%)$$

1,4-Diarylbutadiene derivatives may also be obtained by two different methods.[66,209–211]

$$C_6H_5CH{=\!\!=}CHCHO \div (C_6H_5)_3P{=\!\!=}CHC_6H_5$$

84%

$$C_6H_5CH{=\!\!=}CHCH{=\!\!=}CHC_6H_5$$

63%

$$C_6H_5CHO \div (C_6H_5)_3P{=\!\!=}CHCH{=\!\!=}CHC_6H_5$$

Paths A and B have been used for the synthesis of a large number of unsymmetrically substituted 1,4-diarylbutadienes.[210,211] The symmetrically substituted compounds may also be prepared by a third method in which glyoxal is the starting carbonyl compound.[211]

$$(40\%)$$

A number of 1,1,4-triarylbutadienes was prepared from the alkylidene phosphorane 113.[211] For example,

$$C_6H_5CHO \div (C_6H_5)_3P{=\!\!=}CHCH{=\!\!=}C(C_6H_5)_2 \rightarrow C_6H_5CH{=\!\!=}CHCH{=\!\!=}C(C_6H_5)_2$$
$$\textbf{113}$$

The same diene is formed in 64% yield by the action of cinnamylidenetriphenylphosphorane (114) on benzophenone.[125]

$$(C_6H_5)_2C{=\!\!=}O - (C_6H_5)_3P{=\!\!=}CHCH{=\!\!=}CHC_6H_5 \rightarrow$$
$$\textbf{114}$$
$$C_6H_5CH{=\!\!=}CH{-\!\!-}CH{=\!\!=}C(C_6H_5)_2$$

p-Bis-(4-arylbutadienyl)benzenes have been prepared by starting from bifunctional ylides[65,210] and from bifunctional carbonyl compounds.[65,211] The synthesis of p-bis-4-phenylbutadienylbenzene (115) is an example of the first route,[210] and the synthesis of p-bis(4,4-diphenylbutadienyl)-

$$2C_6H_5CH=CHCHO + (C_6H_5)_3P=CH \underset{112}{\underset{|}{\bigcirc}} CH=P(C_6H_5)_3 \xrightarrow{(59\%)}$$

$$C_6H_5CH=CHCH=CH \underset{115}{\underset{|}{\bigcirc}} CH=CHCH=CHC_6H_5$$
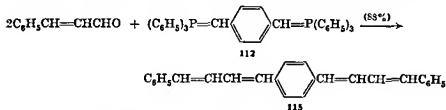
benzene (116) is an example of the second.[211]

$$OHC \underset{|}{\bigcirc} CHO + 2(C_6H_5)_3P=CHCH=C(C_6H_5)_2 \xrightarrow{(57\%)}$$

$$(C_6H_5)_2C=CHCH=CH \underset{116}{\underset{|}{\bigcirc}} CH=CHCH=C(C_6H_5)_2$$
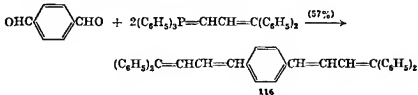
The synthesis of higher diarylpolyenes is effected in basically the same way, starting either from bifunctional ylides or from dicarbonyl compounds as illustrated by the synthesis of 1,10-diphenyldecapentaene (117)[209,212] and its dimethyl derivative 118[209] by two different methods.

$$2C_6H_5CH=CHCHO + (C_6H_5)_3P=CHCH=CHCH=P(C_6H_5)_3 \rightarrow$$

$$\underset{117}{C_6H_5 \diagdown \diagup C_6H_5}$$

$$OHC \diagdown \diagup \overset{CHO}{\diagup} + 2(C_6H_5)_3P=CHC_6H_5 \rightarrow$$

$$\underset{118}{C_6H_5 \diagdown \diagup C_6H_5}$$
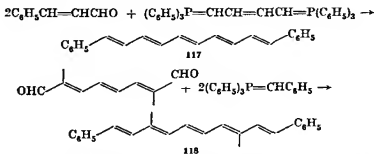
Finally, the preparation of the cross-conjugated chromophore systems 119 has been reported.[213]

$$C_6H_5(CH=CH)_nCO(CH=CH)_{n'}C_6H_5 + (C_6H_5)_3P=CH(CH=CH)_{n'}C_6H_5 \rightarrow$$

$$C_6H_5(CH=CH)_nC \underset{\underset{CH(CH=CH)_{n'}C_6H_5}{\|}}{\overset{(CH=CH)_{n'}C_6H_5}{}}$$

119 ($n=1,2, n'=0.1,2, n''=0.1$)
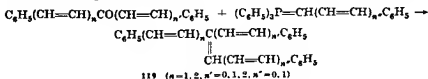
[210] Heitman, Sperna Weiland, and Huisman, Koninkl. Ned. Akad. Wetenschap., Proc., Ser. B., 64, 165 (1961) [C.A., 55, 17567 (1961)].

[211] Bohlmann, Chem. Ber., 89, 2191 (1956)

(path A), no isomerization of the double bond took place and the *trans* isomer was obtained exclusively in 69% yield.   Path B, on the other hand, gave 58% of a mixture containing 55% *trans-* and 45% *cis*-phenylbutadiene.

1,1-Diphenylbutadiene was prepared from β-phenylcinnamaldehyde by using path A.[128]
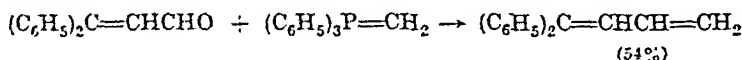
$$(C_6H_5)_2C{=}CHCHO \,+\, (C_6H_5)_3P{=}CH_2 \,\rightarrow\, (C_6H_5)_2C{=}CHCH{=}CH_2$$
$$(54\%)$$

1,4-Diarylbutadiene derivatives may also be obtained by two different methods.[66,209–211]

$$C_6H_5CH{=}CHCHO \,+\, (C_6H_5)_3P{=}CHC_6H_5$$

84%

$$C_6H_5CH{=}CHCH{=}CHC_6H_5$$

63%

$$C_6H_5CHO \,+\, (C_6H_5)_3P{=}CHCH{=}CHC_6H_5$$

Paths A and B have been used for the synthesis of a large number of unsymmetrically substituted 1,4-diarylbutadienes.[210,211]   The symmetrically substituted compounds may also be prepared by a third method in which glyoxal is the starting carbonyl compound.[211]

$$(40\%)$$

A number of 1,1,4-triarylbutadienes was prepared from the alkylidene phosphorane 113.[211]   For example,

$$C_6H_5CHO \,+\, (C_6H_5)_2P{=}CHCH{=}C(C_6H_5)_2 \,\rightarrow\, C_6H_5CH{=}CHCH{=}C(C_6H_5)_2$$
$$\mathbf{113}$$

The same diene is formed in 64% yield by the action of cinnamylidene-triphenylphosphorane (114) on benzophenone.[128]

$$(C_6H_5)_2C{=}O \,+\, (C_6H_5)_3P{=}CHCH{=}CHC_6H_5 \,\rightarrow\,$$
$$\mathbf{114}$$
$$C_6H_5CH{=}CH{-}CH{=}C(C_6H_5)_2$$

Allenes can also be prepared by the Wittig reaction. Again, two methods may be used for the preparation of tetraphenylallene. Path A

$$(C_6H_5)_2C\!=\!C\!=\!O \;+\; (C_6H_5)_3P\!=\!C(C_6H_5)_2$$

$$(C_6H_5)_2C\!=\!C\!=\!C(C_6H_5)_2$$

$$(C_6H_5)_2C\!=\!O \;+\; (C_6H_5)_3P\!=\!C\!=\!C(C_6H_5)_2$$
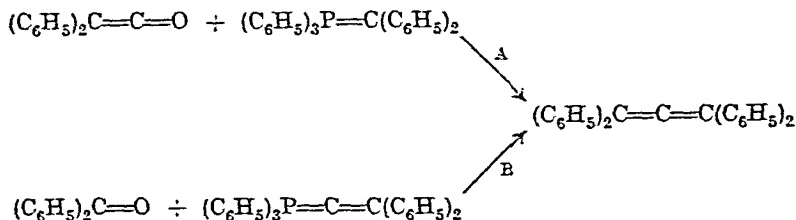
uses diphenylketene and diphenylmethylenetriphenylphosphorane.[9] Path B, which employs milder conditions, gives tetraphenylallene in 54% yield.[123] This was the first use of a vinylidene phosphorane in a Wittig reaction. Using path A, alkyl-substituted allenes such as 1,1-dimethyl-3,3-diphenylallene (120) may be prepared by dry distillation of the preformed, exceedingly stable betaine 64.[150]

$$\begin{array}{c} \overset{\ominus}{(C_6H_5)_3\overset{\oplus}{P}}\!-\!C(CH_3)_2 \\ | \\ \overset{\ominus}{O}\!-\!C\!=\!C(C_6H_5)_2 \end{array} \xrightarrow[64\%]{160°} (CH_3)_2C\!=\!C\!=\!C(C_6H_5)_2$$

<div align="center">64   120</div>
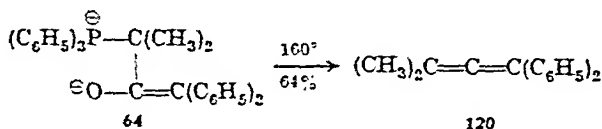
Unsaturated Carbonyl Compounds

Aldehydes. The introduction of an aldehyde group may be effected by the reaction between an alkylidene phosphorane and a dicarbonyl compound in which one carbonyl group has been protected by acetal formation. Subsequent treatment with acid converts the acetal to the aldehyde.[214,215]
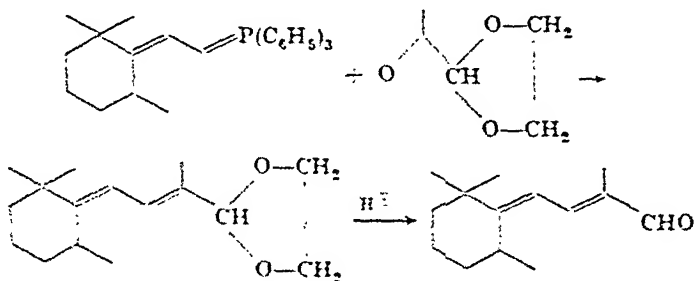
Alternatively, a monocarbonyl compound may be made to react with an alkylidene phosphorane containing an acetal group which is subsequently converted to the aldehyde by treatment with acid.[216] Thus the β-C_{14} aldehyde 121 was converted in 78% yield to the β-C_{19} aldehyde 122.
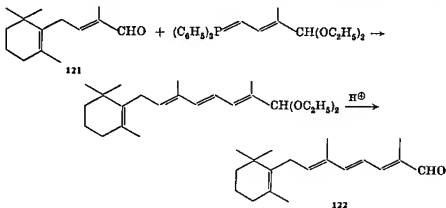
The carbonyl group in resonance-stabilized formylalkylidenetriphenylphosphoranes, for example, 123, need not be protected. Reaction with aldehydes gives α,β-unsaturated aldehydes in good yields.[33,58,115]
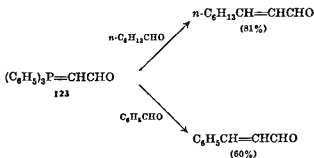
The β,γ-unsaturated aldehyde 125 has been prepared from the enol ester 124, the ester group being subsequently removed by saponification.[217]
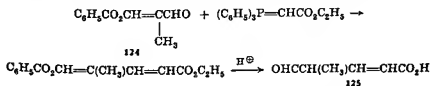
[216] Makin, *Dokl. Akad. Nauk SSSR*, **138**, 387 (1961) [*C.A.*, **55**, 20999 (1961)].

[217] Kucherov, Yanovskaya, and Kovalev, *Dokl. Akad. Nauk SSSR*, **133**, 370 (1960) [*C.A.*, **54**, 24699h (1960)].

Ketones. Unless there is the possibility of a resonance interaction with the ylene double bond, keto groups in alkylidene phosphoranes must be protected, preferably by conversion to a ketal, as illustrated by the synthesis of 7-fluoro-6-methylhept-5-en-2-one (126).[218]

$$CH_2FCOCH_3 + (C_6H_5)_3P{=}CHCH_2CH_2{-}\overset{\displaystyle O\qquad O}{\underset{\displaystyle CH_2{-}CH_2}{C{-}CH_3}} \rightarrow$$

$$\overset{\displaystyle CH_3}{\underset{\displaystyle \underset{CH_2{-}CH_2}{O\quad O}}{CH_2FC{=}CH(CH_2)_2{-}C{-}CH_3}} \xrightarrow{\text{H}^{\ominus}} \overset{\displaystyle CH_3}{CH_2FC{=}CHCH_2CH_2COCH_3}$$

$$\text{126}$$
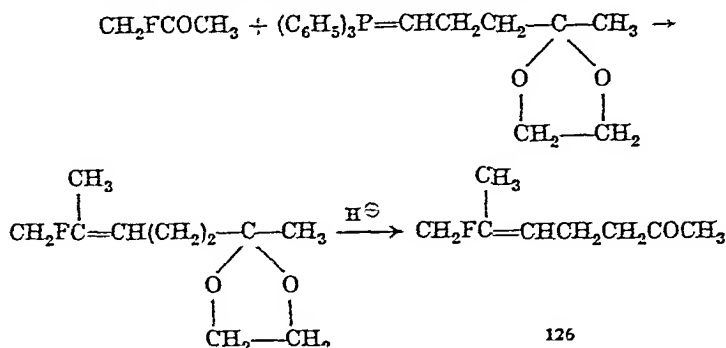
Acylmethylene phosphoranes, on the other hand, are stable and may be used directly in the synthesis of α,β-unsaturated ketones.[31]

$$C_6H_5CHO + (C_6H_5)_3P{=}CHCOR \rightarrow C_6H_5CH{=}CHCOR$$
$$(R = CH_3, C_6H_5)$$

$$p\text{-}O_2NC_6H_4CHO + (C_6H_5)_3P{=}CHCOCH_3 \rightarrow p\text{-}O_2NC_6H_4CH{=}CHCOCH_3$$
$$(92\%) \qquad \text{(Ref. 42)}$$
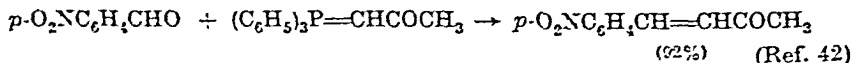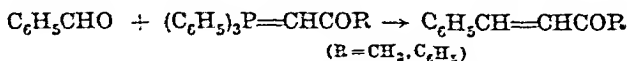
Reactions of ketones with acylmethylene triphenylphosphoranes, as with all other resonance-stabilized ylides, take place less readily.[31] An exception is the formation of the unsaturated fluoroketone 127 in 93% yield.[219]

$$(CF_3)_2C{=}O + (C_6H_5)_3P{=}CHCOCH_3 \rightarrow (CF_3)_2C{=}CHCOCH_3$$
$$\text{127}$$
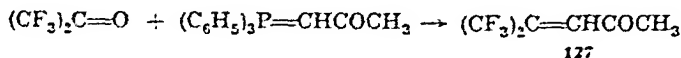
α,β-Unsaturated ketones substituted on the α-position are accessible in a similar way, as illustrated by the preparation of the ketone 128.[32]

$$C_6H_5CHO + (C_6H_5)_3P{=}C(CH_3)COCH{=}CHC_6H_5 \rightarrow$$
$$C_6H_5CH{=}C(CH_3)COCH{=}CHC_6H_5$$
$$\text{128 (51\%)}$$
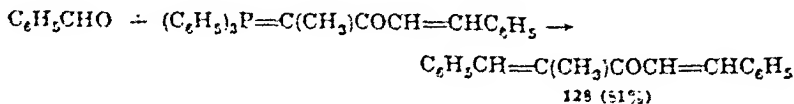
α-Halo-α,β-unsaturated ketones have also been prepared by this method: forcing conditions are required.[59,60] The highest yields were obtained by using excess aldehyde as the solvent. No reaction was

observed when α-haloacylmethylene triphenylphosphoranes were heated with ketones in benzene for several hours.[59]

$$C_6H_5CHO + (C_6H_5)_3P=CCOC_6H_5 \xrightarrow[\text{2 days}]{100°} C_6H_5CH=CCOC_6H_5$$

with Cl below each phosphorane carbon.

(Quant.)   (Ref. 60)
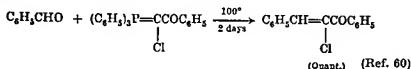
Carboxylic Esters and Other Acid Derivatives. The interaction of carbalkoxymethylene triphenylphosphoranes with carbonyl compounds leads to α,β-unsaturated carboxylic esters. Aldehydes react very readily, as illustrated by the preparation of ethyl cinnamate.[2] Analogously,

$$C_6H_5CHO + (C_6H_5)_3P=CHCO_2C_2H_5 \rightarrow C_6H_5CH=CHCO_2C_2H_5$$

(77%)
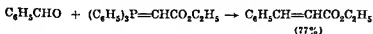
good yields of nitrocinnamic esters were obtained from o-, m-, and p-nitrobenzaldehyde.[162]

The successful reaction of carbethoxymethylenetriphenylphosphorane with heterocyclic aldehydes such as furfural,[220] pyridine aldehydes,[34] and 8-xanthinecarboxaldehyde[221] has also been reported.

Aliphatic aldehydes are also easily converted to α,β-unsaturated carboxylic esters, as illustrated by the preparation of 1,9-bis(methoxycarbonyl)decene (129).[161]

$$CH_3O_2C(CH_2)_8CHO + (C_6H_5)_3P=CHCO_2CH_3 \rightarrow$$
$$CH_3O_2C(CH_2)_8CH=CHCO_2CH_3$$
129 (85%)
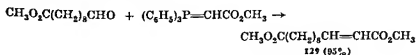
Reactions of ketones with carbalkoxymethylene triphenylphosphoranes occur, as a rule, much less readily. The ease of reaction of fluoroacetone is an exception.[213]

$$\begin{array}{c} CH_2F \\ | \\ C=O \\ | \\ CH_2F \end{array} + (C_6H_5)_3P=CHCO_2C_2H_5 \rightarrow \begin{array}{c} CH_2F \\ | \\ C=CHCO_2C_2H_5 \\ | \\ CH_2F \end{array}$$
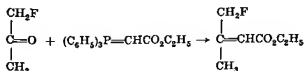
Aromatic or aliphatic ketones, however, will give satisfactory yields in their reactions with carbalkoxymethylene triphenylphosphoranes only

[220] Kucherov, Kovalev, Nazarova, and Yanovskaya, Izv. Akad Nauk SSSR, Otd. Khim. Nauk, 1960, 1512 [C.A., 55, 1420b (1961)].

[221] Bredereck and Fühlusch, Chem Ber., 95, 414 (1962).

after reaction times of several days at room temperature[34] or several hours
at 100–170°.[35]   Thus the ketone **130** reacts slowly in ethanol at 20° with
carbethoxymethylenetriphenylphosphorane to give the ester **131** in 90 %
yield after several days.[34]

$$N\text{—}\underset{\underset{\textbf{130}}{}}{\overset{\overset{CH_3}{|}}{C}}{=}O \ + \ (C_6H_5)_3P{=}CHCO_2C_2H_5 \ \rightarrow \ N\text{—}\underset{\underset{\textbf{131}}{}}{\overset{\overset{CH_3}{|}}{C}}{=}CHCO_2C_2H_5$$
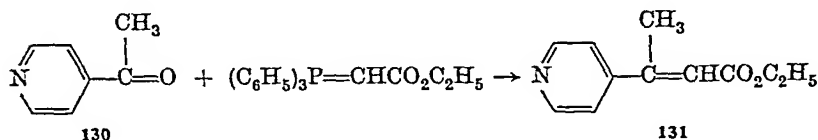
Heating the same ylide with acetophenone without a solvent gives ethyl
β-methylcinnamate in 58 % yield.[35]

$$C_6H_5\underset{}{\overset{\overset{CH_3}{|}}{C}}{=}O \ + \ (C_6H_5)_3P{=}CHCO_2C_2H_5 \ \xrightarrow[\text{10 hr.}]{170°} \ C_6H_5\underset{}{\overset{\overset{CH_3}{|}}{C}}{=}CHCO_2C_2H_5$$
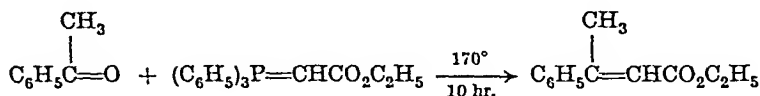
The preparation of esters containing exocyclic double bonds from
cyclic ketones also requires forcing conditions.[34,35]   Ethyl cyclohexyli-
deneacetate (**132**) is formed in 44 % yield in ethanol solution at room
temperature within 1 week;[34] heating the reactants without solvent to
170° for 10 hours gives a yield of 60 %.[35]

$$\bigcirc{=}O \ + \ (C_6H_5)_3P{=}CHCO_2C_2H_5 \ \rightarrow \ \bigcirc{=}CHCO_2C_2H_5$$
$$\textbf{132}$$
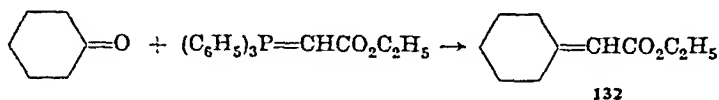
Substituents in the α-position to the carbonyl group further reduce the
reactivity of ketones.   Thus 61 % of the ketone was recovered when a
mixture of 2-methylcyclohexanone and carbethoxymethylenetriphenyl-
phosphorane was kept at room temperature for 12 days; the yield of
ethyl 2-methylcyclohexylideneacetate (**133**) was only 7 %.[34]

$$\overset{CH_3}{\bigcirc}{=}O \ - \ (C_6H_5)_3P{=}CHCO_2C_2H_5 \ \rightarrow \ \overset{CH_3}{\bigcirc}{=}CHCO_2C_2H_5$$
$$\textbf{133}$$
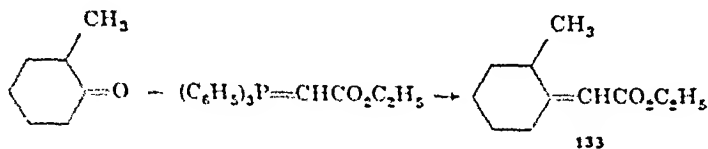
In general, it is advantageous to use high temperatures and little or no solvent when sterically hindered ketones are employed.[36] Thus, in the reaction of 2-methylcyclohexanone mentioned above, the yield of the ester 133 was increased to 30% by heating the reactants without solvent to 150°.[36] Under the same conditions, the tricyclic compound 134 could be obtained in 58% yield.[36]

$$CH_3O, CH_3O \quad \text{(fused ring system)}\quad N{-}C_2H_5, \text{=O} \quad + \quad (C_6H_5)_3P\!=\!CHCO_2CH_3 \rightarrow$$

134
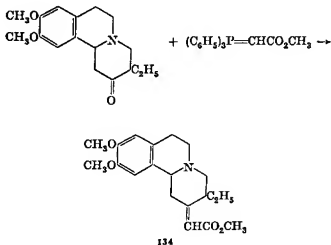
Reactions like these take place much more readily in the presence of benzoic acid as a catalyst.[38]

Substitution of phenyl groups on phosphorus by electron-releasing groups also results, under otherwise equal conditions, in an increase of the yields.[28,58,222-225]

In the reactions of dicarbonyl compounds with 1 mole of carbomethoxy-methylenetriphenylphosphorane, it is usually possible to isolate the compound resulting from conversion of only one carbonyl group to an olefin.[227-229] Thus the monoketone 136 is obtained in 93% yield by the

[221] Trippett and Walker, *Chem. Ind. (London)*, 1960, 933.
[222] Horner, Hoffmann, and Wippel, *Chem. Ber.*, 91, 61 (1958).
[223] Horner, Hoffmann, Wippel, and Klahre, *Chem. Ber.*, 92, 2499 (1959).
[224] Horner, Hoffmann, Klink, Ertel, and Toscano, *Chem. Ber.*, 95, 581 (1962).
[225] Wadsworth, Jr., and Emmons, *J. Am. Chem. Soc.*, 83, 1733 (1961).
[226] Cava and Pohl, *J. Am. Chem. Soc.*, 82, 5242 (1960).
[227] Eiter, *Angew. Chem.*, 73, 619 (1961).
[228] Eiter, *Ann.*, 658, 91 (1962).

interaction of benzocyclobutenedione (135) with 1 mole of ylide, whereas with 2 moles of ylide the final product 137 is formed in 85% yield.[227]
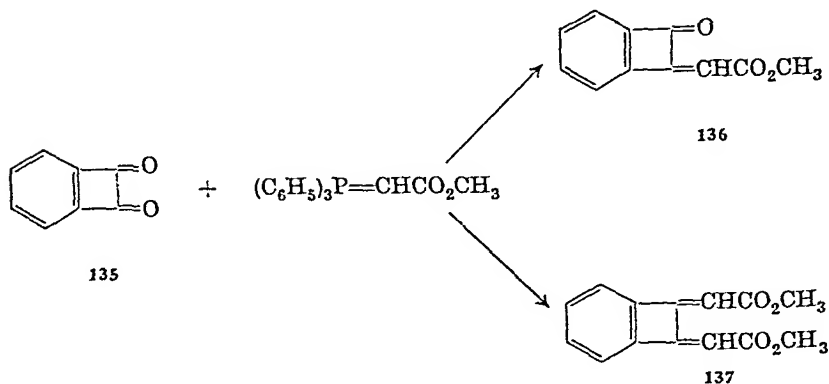
Unsaturated dialdehydes such as *138* lead to polyene dicarboxylic esters, as illustrated by the synthesis of the ester *139*.[230] Methylbixin,
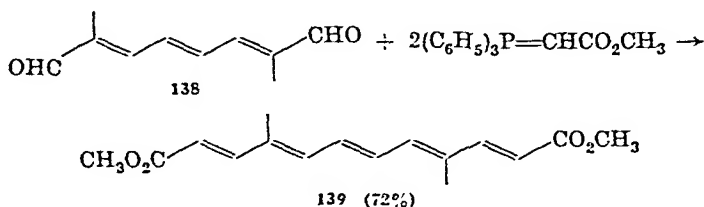
crocetin dimethyl ester[39.231–235] and a large number of other polyene dicarboxylic esters[163.236] have been prepared in this way.

In compounds containing both a keto and an aldehyde group, the latter reacts preferentially. If conversion of the keto group to an olefin is to be effected, the aldehyde group must be protected by acetal formation, as illustrated by the reaction of the carbonyl compound 140 with carbomethoxymethylenetriphenylphosphorane.[237]

In the ketone 140, a hydroxyl group has also been protected by conversion to its tetrahydropyranyl ether. Two neighboring hydroxyl groups, as in

<div align="center">140</div>

<div align="center">(60%)</div>
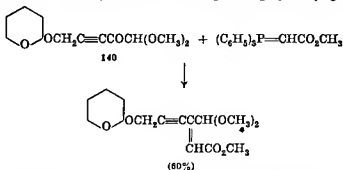
sugars, may also be blocked by ketal formation, as shown by the interaction of the dimethylketal of D-glyceraldehyde with carbethoxymethylenetriphenylphosphorane to form the ester 141.[238]

<div align="center">141 (75%)</div>
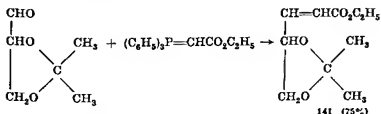
Polyene aldehydes react with carbalkoxymethylene triphenylphosphoranes to form polyene carboxylic esters which contain one more double bond than the aldehyde. For $n = 1$ through 4, the yields are

$$CH_3(CH=CH)_nCHO + (C_6H_5)_3P=CHCO_2C_2H_5 \rightarrow$$
$$CH_3(CH=CH)_{n+1}CO_2C_2H_5 \rightarrow$$
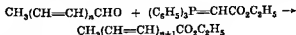
higher than 80%.[239]

Polyene aldehydes containing triple bonds may also be employed in this reaction,[239] which has been used extensively for the synthesis of

$$CH_2=CC=CCH=CHCHO + (C_6H_5)_3P=CHCO_2C_2H_5 \rightarrow$$
<div align="center">CH_3 CH_3</div>

$$CH_3=CC=CCH=CHCH=CHCO_2C_2H_5$$
<div align="center">CH_3 CH_3</div>
<div align="center">(65%)</div>
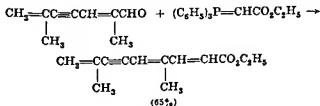
carboxylic esters in the carotene series.

[238] Kuhn and Brossmer, *Angew. Chem.*, 74, 252 (1962).

[239] Yanovskaya, Kucherov, and Kovalev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1962, 674 [*C.A.*, 57, 16379a (1962)].

α,β-Unsaturated carboxylic esters may also be obtained from a glyoxylic ester or its vinylogs, as illustrated by the preparation of ethyl β-ionylidene-acetate (142).[240]

142
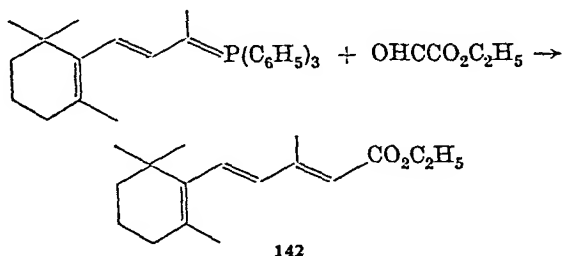
In order to prevent side reactions involving the ester group, it has been proposed to add the ylide solutions to the aldehyde and not vice versa. This procedure furnished the unsaturated ester 143 in 46% yield.[241]

$$n\text{-}C_3H_7(C\equiv C)_2CH_2CH_2CH=P(C_6H_5)_3 + OHCCH=CHCO_2CH_3 \rightarrow$$
$$n\text{-}C_3H_7(C\equiv C)_2CH_2CH_2(CH=CH)_2CO_2CH_3$$
143
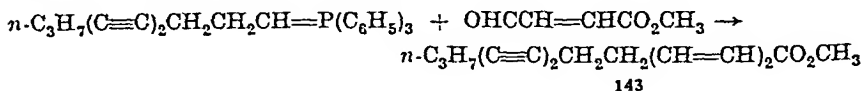
Instead of a vinylog of glyoxylic ester, a vinylog of a carbalkoxy-methylenephosphorane may also be used as illustrated by the reaction of substituted benzaldehydes with the phosphorane 144.[242] The phosphorane 144 is easily accessible from methyl γ-bromocrotonate. A
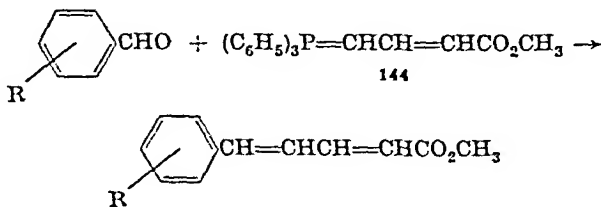
comparison of the results obtained by this reaction with those obtained in the Reformatsky reaction showed that the Wittig reaction is definitely to be preferred, especially with benzaldehydes containing nitro, dimethyl-amino, or chloro substituents. Even when comparable yields are obtained by both methods, the Wittig reaction has the advantages of convenience and speed. By using ultraviolet spectroscopy it was shown that the reaction was practically complete after 5 minutes. The only exception occurs in reactions using 2,4,6-trimethoxybenzaldehyde for which the

[240] Pommer and Sarnecki, Ger. pat. 1,068,706 (to BASF) [C.A., 56, 512a (1962)].
[241] Bohlmann and Inhoffen, Chem. Ber., 89, 1276 (1956).
[242] Bohlmann, Chem. Ber., 90, 1519 (1957).

Reformatsky reaction is superior.   It is of interest to note that aldehydes containing *o*-hydroxyl groups can also be employed in the Wittig reaction.

The reaction between aldehydes and carbalkoxy ylides containing α-alkyl substituents leads to α-branched α,β-unsaturated carboxylic esters.   Thus cinnamaldehyde and the phosphorane 145 give the α-substituted ester 146.[40,111]   The vinylogous ylide 147 furnishes the corresponding hexatrienecarboxylic ester 148.[232,235]   By employing this

$$C_6H_5CH=CHCHO + (C_6H_5)_3P=CCO_2CH_3 \rightarrow C_6H_5CH=CHCH=CCO_2CH_3$$
$$\underset{\substack{|\\ CH_2C_6H_5}}{} \qquad \underset{\substack{|\\ CH_2C_6H_5}}{}$$

$$\underset{145}{} \qquad \qquad \underset{146\ (83\%)}{}$$

$$C_6H_5CH=CHCHO + (C_6H_5)_3P=CHCH=CCO_2CH_3 \rightarrow$$
$$\underset{\substack{|\\ CH_3}}{}$$
$$\underset{147}{}$$

$$C_6H_5CH=CHCH=CHCH=CCO_2CH_3$$
$$\underset{\substack{|\\ CH_3}}{}$$
$$\underset{148\ (70\%)}{}$$
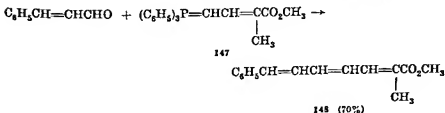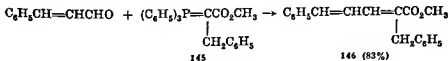
method and starting from polyene dialdehydes, branched polyene dicarboxylic esters have been prepared.[39]

Whereas in all these reactions using resonance-stabilized phosphoranes the *trans* olefin is formed predominantly, interaction of reactive ylides with α-keto esters leading to α-branched α,β-unsaturated esters always yields a considerable amount of the *cis* isomers.[164]

$$RCHO + (C_6H_5)_3P=CCO_2CH_3$$
$$\underset{\substack{|\\ R'}}{}$$
$$\searrow$$
$$RCH=CCO_2CH_3$$
$$\underset{\substack{|\\ R'}}{}$$
$$\nearrow$$
$$RCH=P(C_6H_5)_3 + O=CCO_2CH_3$$
$$\underset{\substack{|\\ R'}}{}$$
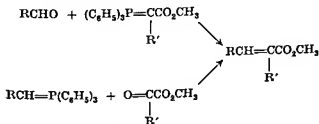
Similarly, α-halo-α,β-unsaturated carboxylic esters[60,117] are prepared from halocarbomethoxymethylene triphenylphosphoranes and aldehydes, as illustrated by the synthesis of the ester 149.[117]

$$C_6H_5CH=CHCHO + (C_6H_5)_3P=CCO_2CH_3 \rightarrow C_6H_5CH=CHCH=CCO_2CH_3$$
$$\underset{\substack{|\\ Br}}{} \qquad \qquad \underset{\substack{|\\ Br}}{}$$
$$\underset{149\ (Quant.)}{}$$
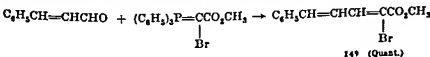
α-Halo-α,β-unsaturated carboxylic esters that easily eliminate hydrogen halide furnish substituted propiolic acids on saponification.[117]

$$C_6H_5CHO + (C_6H_5)_3P{=}CCO_2CH_3 \rightarrow$$
$$\underset{Br}{|}$$

$$C_6H_5CH{=}CCO_2CH_3 \xrightarrow{OH^{\ominus}} C_6H_5C{\equiv}CCO_2H$$
$$\underset{Br}{|}$$

(82%)
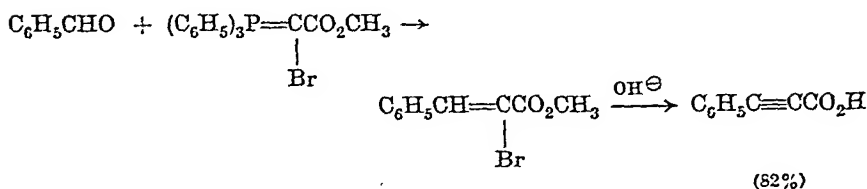
Esters of ω-hydroxy-α,β-unsaturated carboxylic acids (150) are formed by the interaction of 2-hydroxytetrahydropyran with carbalkoxy-alkylidene triphenylphosphoranes.[114]   The *trans* isomer is formed almost exclusively.

$$\underset{O}{\bigcirc}{-}OH + (C_6H_5)_3P{=}CCO_2R' \rightarrow HO(CH_2)_4CH{=}CCO_2R'$$
$$\underset{R}{|} \qquad\qquad\qquad \underset{R}{|}$$
$$\mathbf{150}$$
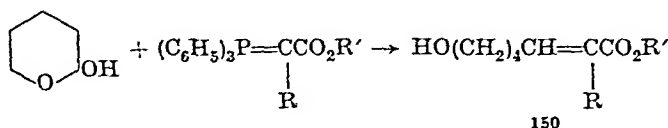
cis-Carboxylic esters are obtained only if there is no possibility for resonance interaction between the ester group and the ylene double bond.   By using dimethylformamide as the solvent and preferably in the presence of iodide ion, the *cis* compounds are formed almost exclusively.[114,170,171]   Pelargonaldehyde and the ylide 151, for instance, give ethyl oleate (152) stereospecifically in 73% yield.[114,170]   Probably as a

$$CH_3(CH_2)_7CHO + (C_6H_5)_3P{=}CH(CH_2)_7CO_2C_2H_5 \xrightarrow[I^{\ominus}]{DMF}$$
$$\mathbf{151}$$

$$\overset{H}{\underset{CH_3(CH_2)_7}{\diagdown}}C{=}C\overset{H}{\underset{(CH_2)_7CO_2C_2H_5}{\diagup}}$$
$$\mathbf{152}$$
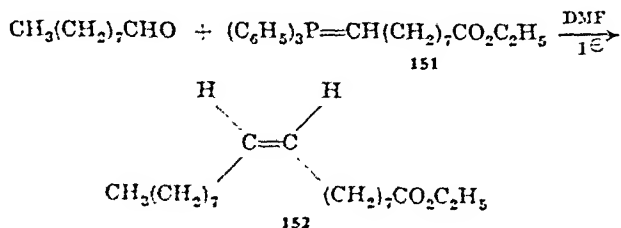
consequence of the solvation of this ylide in the polar solvent, the ester group in the reactive phosphorane 151 remains essentially unattacked. In other circumstances an ester group remote from the ylide portion of the molecule may, however, be attacked.[205]

Ethyl α-eleostearate (153) was also synthesized from the ylide 151.[114]

$$CH_3(CH_2)_3 \quad H$$
$$C=C$$
$$H \qquad C=C$$
$$H \qquad CHO$$
$$+ \quad (C_6H_5)_3P=CH(CH_2)_7CO_2C_2H_5 \quad \xrightarrow{I^\ominus}$$
$$\mathbf{151}$$

$$CH_3(CH_2)_3 \quad H$$
$$C=C$$
$$H \qquad C=C$$
$$H \qquad (CH_2)_7CO_2C_2H_5$$
$$C=C$$
$$H \qquad H$$
$$\mathbf{153}$$
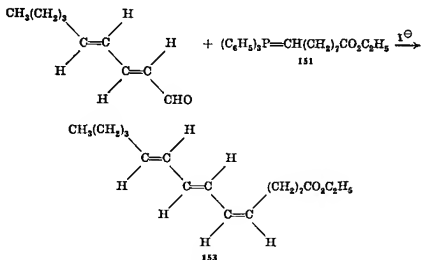
Again, this type of compound may be prepared by two different ways, as illustrated by the synthesis of the biologically important acids of the *cis-cis*-divinylmethane type.[114]

$$R \quad CH_2CHO$$
$$C=C$$
$$H \qquad H$$
$$+ \quad (C_6H_5)_3P=CH(CH_2)_nCO_2CH_3$$

$$\downarrow I^\ominus$$

$$R \quad CH_2 \quad (CH_2)_nCO_2CH_3$$
$$C=C \qquad C=C$$
$$H \qquad H \quad H \quad H$$

$$\uparrow I^\ominus$$

$$R \quad CH_2CH=P(C_6H_5)_3$$
$$C=C$$
$$H \qquad H$$
$$+ \quad OHC(CH_2)_nCO_2CH_3$$
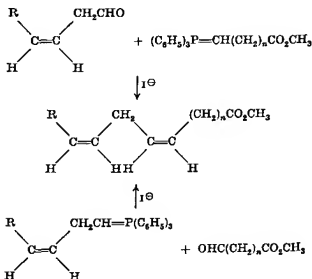
The reaction between ketones and alkylidene phosphoranes of the type 154 is not stereospecific, but saturated branched fatty acids such as

155 can be obtained in good yield by saponification followed by catalytic hydrogenation.[114]

$$
\begin{array}{c}
CH_3 \\
| \\
CH_3(CH_2)_mC{=}O \ + \ (C_6H_5)_3P{=}CH(CH_2)_nCO_2C_2H_5 \ \rightarrow \\
\mathbf{154}
\end{array}
$$

$$
\begin{array}{cc}
CH_3 & CH_3 \\
| & | \\
CH_3(CH_2)_mC{=}CH(CH_2)_nCO_2C_2H_5 \ \rightarrow \ CH_3(CH_2)_m\overset{}{CH}(CH_2)_{n+1}CO_2H \\
& \mathbf{155}
\end{array}
$$
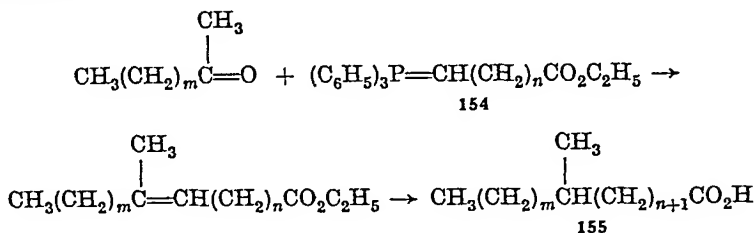
Unsaturated amides and nitriles have also been synthesized. Thus carbamidomethylenetriphenylphosphorane (**156**) reacts with crotonaldehyde to give the amide of sorbic acid,[243] and with benzaldehyde to give cinnamamide.[58]

$$
(C_6H_5)_3P{=}CHCONH_2
\begin{cases}
\xrightarrow{\ CH_3CH=CHCHO\ } CH_3CH{=}CHCH{=}CHCONH_2 \\
\\
\xrightarrow{\ C_6H_5CHO\ } C_6H_5CH{=}CHCONH_2
\end{cases}
$$

156
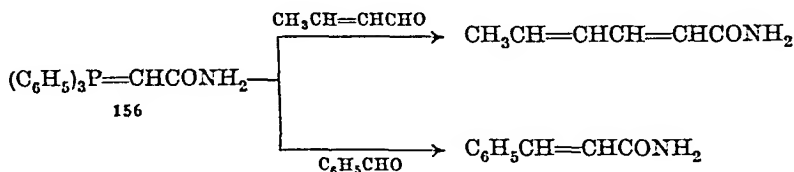
The interaction of cyanomethylenetriphenylphosphorane (**157**) with benzaldehyde and its derivatives gives the corresponding cinnamonitriles in good yields.[42,43,53] p-Nitrocinnamonitrile, for instance, is obtained from p-nitrobenzaldehyde in 74% yield.[42]

$$
p\text{-}O_2NC_6H_4CHO \ + \ (C_6H_5)_3P{=}CHCN \ \rightarrow \ p\text{-}O_2NC_6H_4CH{=}CHCN
$$
157
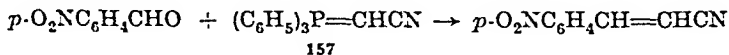
As illustrated by the synthesis of the vitamin A_2 carbonitrile (**158**), vinylogous cyanomethylene triphenylphosphoranes can also be employed as starting materials.[244]

158 (86%)
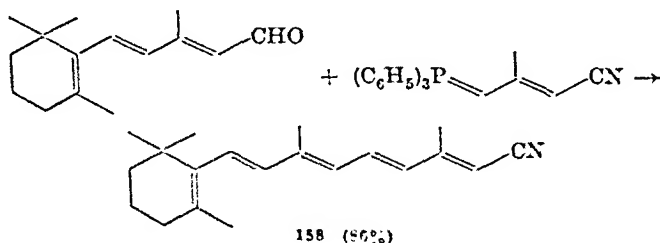
[243] Wittig and Pommer, Ger. pat. 943,648 (to BASF) [C.A., 52, 16292d (1958)].

[244] Enter, Oediger, and Truscheit, Ger. pat. 1,110,633 (to Farbenf. Bayer) [C.A., 56, 3522e (1962)].

Vinyl Halides

Monohaloölefins are formed in the reaction of halomethylene triphenyl-phosphoranes with aldehydes and ketones.[91,92] Benzaldehyde and benzophenone react with chloromethylenetriphenylphosphorane to give the corresponding vinyl halides in 67% yield.[92]

$$(C_6H_5)_3P=CHCl + C_6H_5CHO \rightarrow C_6H_5CH=CHCl$$
$$(C_6H_5)_3P=CHCl + (C_6H_5)_2CO \rightarrow (C_6H_5)_2C=CHCl$$
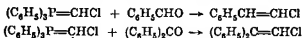
Aliphatic ketones can also be converted to vinyl chlorides.[95,96] If the

(80%)
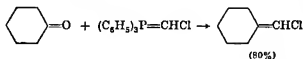
ylides are generated from triphenylphosphine and carbenes, the yields on the average decrease to 30%.[96]

The preparation of vinyl bromides has also been reported. The reaction with β-ionone, for instance, proceeds in 70% yield.[84]
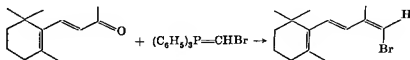
1,1-Dihaloölefins are obtained from dihalomethylene triphenylphos-phoranes.[82,93,94,98] The reactions with dichloromethylenetriphenylphos-phorane are illustrative.
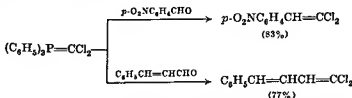
The preparation of mixed haloolefins is exemplified by the reaction of fluorochloromethylenetriphenylphosphorane with benzophenone.[84]

(40%)
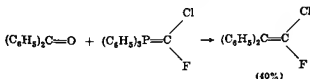
Since carbon tetrachloride[98] and carbon tetrabromide[82] react directly with triphenylphosphine with the formation of dihalomethylene triphenyl-phosphoranes, 1,1-dihaloölefins can be prepared in one step by carrying out this reaction in the presence of carbonyl compounds.

$$CBr_4 + 2(C_6H_5)_3P \longrightarrow (C_6H_5)_3P{=}CBr_2 \xrightarrow{C_6H_5CHO} C_6H_5CH{=}CBr_2$$
$$+ (C_6H_5)_3PBr_2 \qquad\qquad (84\%)$$
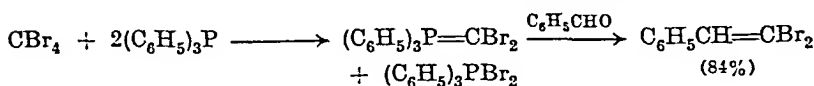
Vinyl Ethers

The synthesis of vinyl ethers is important because they can be converted to aldehydes by saponification. The original procedure consisted of slow addition of formic ester to the alkylidene phosphorane followed by acid hydrolysis of the initially formed enol ether.[113] Hexahydrobenzaldehyde was obtained in moderate yield in this way, which is a general method for
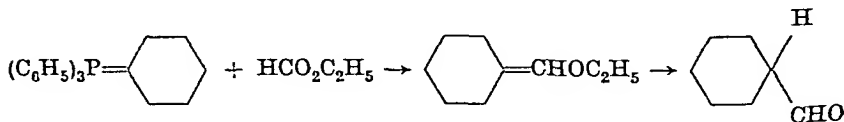
the conversion of a halogen compound to an aldehyde containing one more carbon atom. Since, however, the formic ester is partially cleaved by the ylide into carbon monoxide and alcohol, the yields are usually not very good.[245]

A better synthesis of vinyl ethers involves the reaction of a carbonyl compound with an alkoxymethylene triphenylphosphorane.[92,246-248] For example, benzophenone reacts with methoxymethylenetriphenylphosphorane to give 1,1-diphenylvinyl methyl ether (159) in 83% yield;[247] treatment with acid gives diphenylacetaldehyde.

$$(C_6H_5)_2C{=}O + (C_6H_5)_3P{=}CHOCH_3 \longrightarrow$$
$$(C_6H_5)_2C{=}CHOCH_3 \longrightarrow (C_6H_5)_2CHCHO$$
$$\mathbf{159}$$
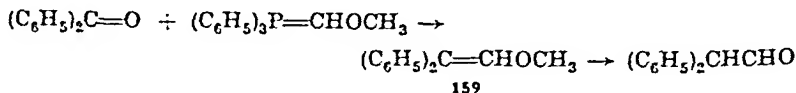
The over-all result is the conversion of a carbonyl compound to an aldehyde containing one more carbon atom. The best reagent for the
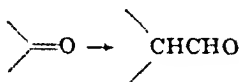
occasionally difficult hydrolysis of the enol ether is perchloric acid in diethyl ether.[248]

Cyclic ketones may also be subjected to this reaction. Cyclohexanone is converted to methoxymethylenecyclohexane which yields hexahydrobenzaldehyde on heating with ethereal perchloric acid.[248]
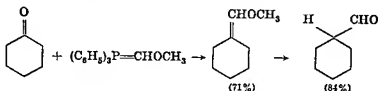
Alkoxymethylene triphenylphosphoranes are relatively unstable at room temperature. It is therefore advantageous to prepare them at as low a temperature as practicable and to add the carbonyl compound before warming the reaction mixture to room temperature.[87] The alkoxide method is of advantage with carbonyl compounds that are stable to alkoxides, as in the synthesis of 160.[92]
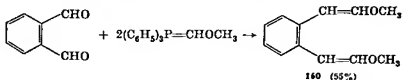
n-Butoxymethylenetriphenylphosphorane is less stable than methoxymethylenetriphenylphosphorane.[87] Low temperatures are therefore particularly important in the synthesis of butyl vinyl ethers. When diethyl ketone was allowed to react with *n*-butoxymethylenetriphenylphosphorane at −40° and the reaction mixture was then left at room temperature for several hours, 1-*n*-butoxy-2-ethylbutene (161) was obtained in 73% yield.[248]

$$(C_2H_5)_2C{=}O \ + \ (C_6H_5)_3P{=}CHOC_4H_9\text{-}n \ \rightarrow$$
$$(C_2H_5)_2C{=}CHOC_4H_9\text{-}n \ \rightarrow \ (C_2H_5)_2CHCHO$$
$$\text{161}$$
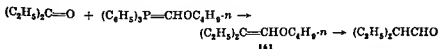
Hydrolysis of the ether with perchloric acid furnished diethylacetaldehyde in 70% yield. Cyclic ketones react analogously.[248]
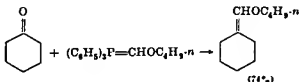
Aryloxymethylene triphenylphosphoranes are more stable than alkoxymethylene triphenylphosphoranes. Vinyl aryl ethers are therefore particularly accessible. For example, p-methylphenoxymethylenecyclohexane (163) is obtained in 82% yield by allowing p-methylphenoxymethylenetriphenylphosphorane (162) to interact with cyclohexanone in ether at room temperature for 2 hours.[248]
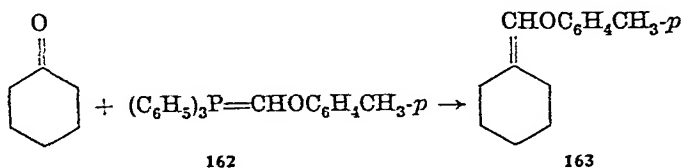
β-(p-Methylphenoxy)styrene (164), obtained similarly in 75% yield from benzaldehyde, could be readily hydrolyzed with perchloric acid[246] to give phenylacetaldehyde in 73% yield.[248]

$$C_6H_5CH{=}CHOC_6H_4CH_3\text{-}p \rightarrow C_6H_5CH_2CHO$$
$$164$$
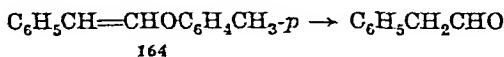
In the same way, diethylacetaldehyde is prepared from diethyl ketone by way of diethylvinyl p-tolyl ether (165).[248]

$$(C_2H_5)_2CO \;\dotplus\; (C_6H_5)_3P{=}CHOC_6H_4CH_3\text{-}p \xrightarrow{\;72\%\;}$$
$$162$$
$$(C_2H_5)_2C{=}CHOC_6H_4CH_3\text{-}p \xrightarrow{\;80\%\;} (C_2H_5)_2CHCHO$$
$$165$$
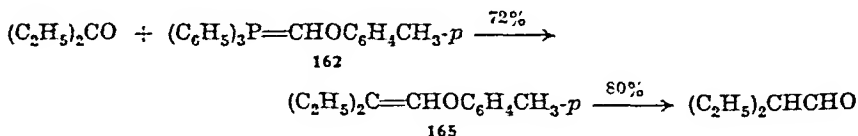
Vinyl phenyl ethers may be obtained from phenoxymethylenetriphenylphosphorane (166).[248]

$$(C_6H_5)_2CO \;\dotplus\; (C_6H_5)_3P{=}CHOC_6H_5 \rightarrow (C_6H_5)_2C{=}CHOC_6H_5$$
$$166 \qquad\qquad (65\%)$$
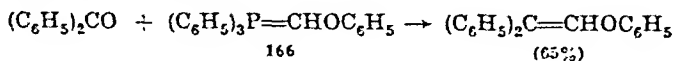
Vinyl thio ethers have also been prepared by this method.[92] They are hydrolyzed to aldehydes much less readily.

$$(C_6H_5)_2CO \;\dotplus\; (C_6H_5)_3P{=}CHSCH_3 \rightarrow (C_6H_5)_2C{=}CHSCH_3$$
$$(84\%)$$
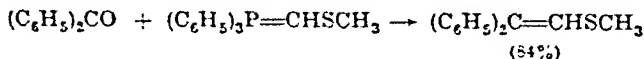
Analytical Applications

The alkylidene phosphorane 167 has been suggested as a specific reagent for the characterization of aldehydes in the presence of ketones.[249-251] In ethanol-water (95:5) at 75° it reacts readily with all aldehydes

investigated but not with ketones. The reactions are complete when the
yellow color of the ylide disappears. In pure ethanol, ketones react to a

$$(C_6H_5)_3P= CH \underset{\textbf{167}}{\underbrace{}} SO_2 \underset{}{\underbrace{}} Br + RCHO \rightarrow$$

$$RCH=CH \underset{}{\underbrace{}} SO_2 \underset{}{\underbrace{}} Br$$
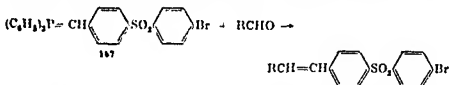
limited extent (5–10%); on addition of 5% water, only aldehydes react
and the yields are between 50% and 90%. The Wittig reagent 167 may
therefore be used for the selective characterization and identification of
aldehydes.

Side Reactions

Fortunately, side reactions occur only rarely and can usually be
suppressed by suitable choice of conditions. The handling of unstable
alkylidene phosphoranes has already been mentioned. Reactions are
either carried out at low temperatures, or the alkoxide method which
permits interaction of the carbonyl compound with the alkylidene
phosphorane *in statu nascendi* is used.

The strongly basic alkylidene phosphoranes can also function as
proton acceptors to remove a proton from the α-position of carbonyl
compounds. This reaction is particularly pronounced with easily
enolizable ketones such as cyclohexanone and cyclopentanone. If the
reaction between the ylide and the carbonyl compound is sterically
hindered, enolization becomes the main reaction [185]
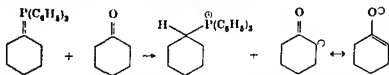
Methoxymethylenetriphenylphosphorane converts cyclopentanone par-
tially to 2-cyclopentylidenecyclopentanone (168).[248]
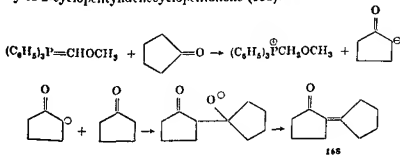
Analogous condensations have been observed to a lesser extent with acetone, which is partially converted to mesityl oxide (169) by Wittig reagents.[182]   Because decreasing temperatures favor the Wittig reaction

$$(C_6H_5)_3P{=}CH_2 + (CH_3)_2CO \longrightarrow (C_6H_5)_3\overset{\ominus}{P}CH_3 + CH_3CO\overset{\ominus}{C}H_2 \xrightarrow{(CH_3)_2CO}$$

$$CH_3COCH_2\underset{\underset{O^{\ominus}}{|}}{C}(CH_3)_2 \longrightarrow \underset{169}{CH_3COCH{=}C(CH_3)_2}$$
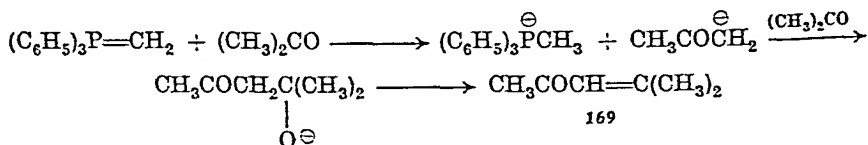
over aldol condensations, reactions with enolizable ketones are best done at low temperatures.[248]

The elimination of acids from reactants or products under the influence of Wittig reagents has also been observed.   An example is the elimination of hydrogen bromide from the diene 170.[16]

170
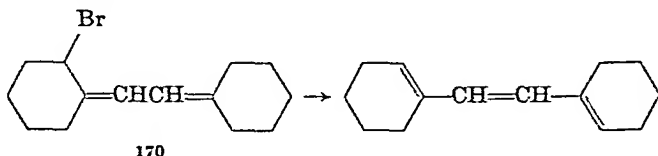
In the reaction of methylenetriphenylphosphorane with the keto steroid 171, the expected product is accompanied by the dienone 172 formed by elimination of acetic acid.[252]

171   172
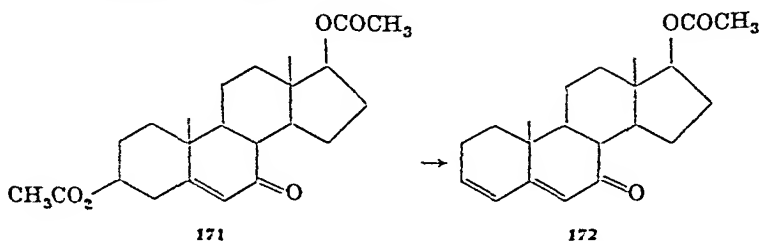
Elimination of acetic acid has also been observed in the reaction of benzylidenetriphenylphosphorane with the ester 173.   1,4-Addition leads to the betaine 174.[253]

173

174
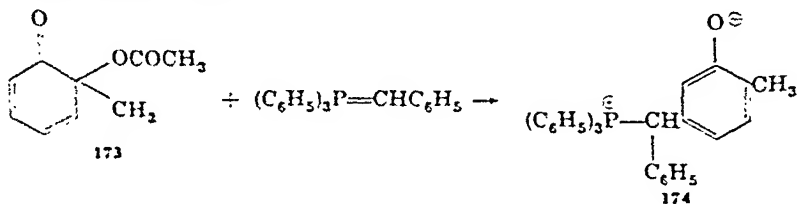
alkylidenephosphorane 175 with methylenecyclohexanone, for which the following mechanism has been assumed.[158]
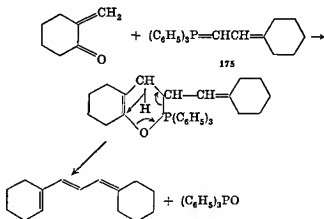
The formation of 1,6-diphenylhexa-1,3,5-triene (178) as a side product in the reaction of ketone 176 with the phosphorane 177 has also been explained on the basis of a 1,4-addition.[213]

$$C_6H_5CH=CHCH=CHCOC_6H_5 + (C_6H_5)_3P=CHCH=CHC_6H_5 \rightarrow$$
$$\underset{176}{} \qquad \underset{177}{}$$

$$C_6H_5CH \equiv CH + C_6H_5(CH=CH)_3C_6H_5 + (C_6H_5)_3PO$$
$$\underset{178}{}$$
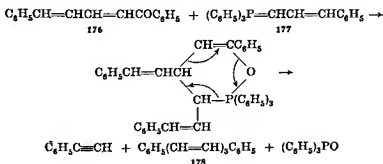
Phenylacetylene could not be detected. An alternative path that has been suggested involves reaction of the ylide 177 with the starting phosphonium salt followed by a Hofmann elimination.[12]

$$C_6H_5(CH=CH)_3C_6H_5 + (C_6H_5)_3P$$
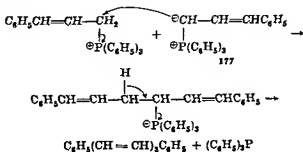
The reaction of methylenetriphenylphosphorane with the sterically hindered mesityl styryl ketone (179) may also be considered as a 1,4-addition. In this reaction, triphenylphosphine rather than triphenylphosphine oxide is eliminated and the cyclopropane 180 is formed.[131]

$$C_6H_5CH=CHC\underset{\parallel}{\overset{}{\text{—}}}\text{—} \quad \div \ (C_6H_5)_3P=CH_2 \ \rightarrow$$

O

$$C_6H_5CH\text{—}CH=C\text{—}$$

CH$_2$ $\ominus$O

$\ominus$P(C$_6$H$_5$)$_3$

$$C_6H_5CH\text{—}CHC\text{—}$$

CH$_2$ O

180   (52%)
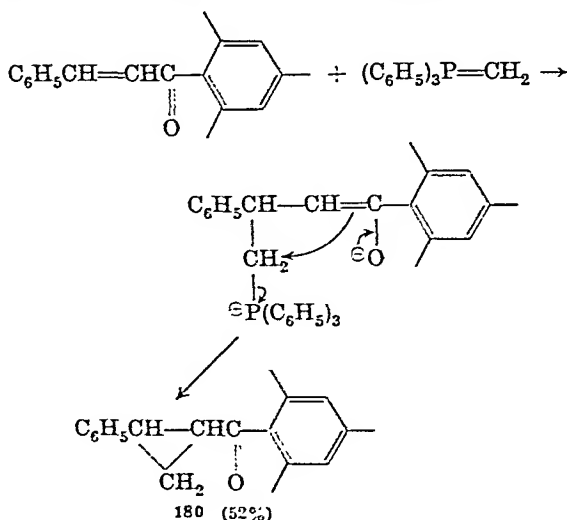
Thus addition to an activated double bond takes place in preference to the Wittig reaction. It is therefore necessary, when the Wittig reaction is used to prepare compounds containing an activated double bond, to avoid an excess of phosphorane in order to prevent subsequent addition of the ylide to the double bond.[130]

As mentioned previously, α-bromoketones such as phenacyl bromide do not undergo Wittig reactions with alkylidene phosphoranes.[106–108]

In compounds that contain both ester and carbonyl groups, the latter react preferentially with Wittig reagents as long as the ylide is not present in excess. The ylide should therefore be added slowly to the carbonyl component.[241]

If an excess of alkylidene phosphorane is used in reactions with compounds such as acetylated steroid keto alcohols,[252–254] the ester group is removed by the ylide by the following process, and the reaction product may have to be reacetylated.

$$(C_6H_5)_3P=CH_2 \ \div \ CH_3CO_2R \ \rightarrow \ (C_6H_5)_3\overset{\ominus}{P}\text{—}CH_2\text{—}\overset{O}{\underset{\underset{CH_3}{|}}{\overset{\parallel}{C}}}\text{—}OR \ \rightarrow$$

$$(C_6H_5)_3\overset{\ominus}{P}\text{—}CH.COCH_3 \ - \ RO^{\ominus}$$
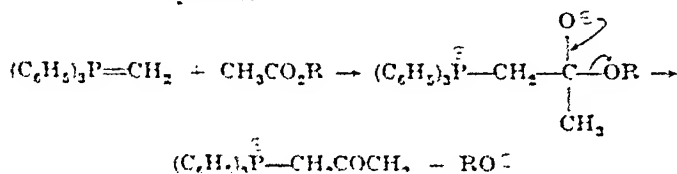
A similar side reaction occurred to a lesser extent in the interaction of allylidenetriphenylphosphorane (181) with N-methylformanilide. Formation of 1-methylanilino-1,3-butadiene (182) is accompanied by elimination of methylanilide anion.[255]

$$C_6H_5NCHO + (C_6H_5)_3P=CHCH=CH_2 \rightarrow$$
$$\underset{|}{\overset{}{CH_3}} \quad\quad\quad\quad 181$$

$$(C_6H_5)_3\overset{\oplus}{P}-CHCH=CH_2$$
$$\underset{\ominus}{O}-CH \cdot N C_6H_5 \rightarrow C_6H_5NCH=CHCH=CH_2$$
$$\underset{|}{\overset{}{CH_3}} \quad\quad\quad\quad\quad CH_3 \quad 182$$

$$(C_6H_5)_3\overset{\oplus}{P}-CHCH=CH_2 + \overset{\ominus}{N}-C_6H_5$$
$$\underset{|}{\overset{}{CHO}} \quad\quad\quad\quad\quad \underset{|}{\overset{}{CH_3}}$$
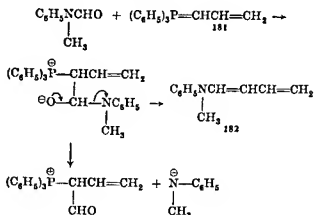
An abnormal decomposition of the betaine has also been observed in the reaction of n-butoxymethylenetriphenylphosphorane with butyraldehyde, in which formation of the expected 1-n-butoxy-1-pentene (183) is accompanied by a hydride shift which gives mostly 1-n-butoxy-pentan-2-one (184).[57]

$$n\text{-}C_3H_7CHO + (C_6H_5)_3P=CHOC_4H_9\text{-}n \longrightarrow$$

$$\underset{|}{\overset{H}{\underset{|}{}}}$$
$$n\text{-}C_3H_7-\overset{}{\underset{|}{C}}-CHOC_4H_9\text{-}n \xrightarrow{12\%} n\text{-}C_3H_7CH=CHOC_4H_9\text{-}n$$
$$\underset{\ominus O}{\overset{}{}} \overset{\oplus}{P}(C_6H_5)_3 \quad\quad\quad\quad\quad 183$$

$$\downarrow 26\%$$

$$n\text{-}C_3H_7CCH_2OC_4H_9\text{-}n$$
$$\underset{O}{\overset{\|}{}}$$
$$184$$

If the oxygen in the betaine may interact with a silicon or a phosphorus atom, attack on silicon occurs preferentially as in the accompanying reaction sequence.[123] The ylide 185 so formed reacts with excess

[255] Wittig and Sommer, *Ann.*, 594, 1 (1955).

benzophenone in a normal Wittig reaction to give tetraphenylallene (186), which was isolated in 28% yield.

$$(C_6H_5)_3P=CH-Si(CH_3)_3 + (C_6H_5)_2CO \rightarrow (C_6H_5)_3\overset{\ominus}{P}-CH-Si(CH_3)_3 \rightarrow$$
$$(C_6H_5)_2C-O^\ominus$$

$$(C_6H_5)_3\overset{\ominus}{P}-CH=C(C_6H_5)_2 + (CH_3)_3SiO^\ominus \rightarrow$$
$$(C_6H_5)_3P=C=C(C_6H_5)_2 + (CH_3)_3SiOH$$
$$\mathbf{185}$$
$$\downarrow (C_6H_5)_2CO$$
$$(C_6H_5)_2C=C=C(C_6H_5)_2$$
$$\mathbf{186}$$

The decisive influence on the course of a Wittig reaction exerted by the halide ion in the phosphonium salt is understandable in terms of the fact that different halide ions can shield the ylide phosphorus atom by complex formation to a different extent.[114] Thus methylenecyclopentane could not be obtained starting from triphenylmethylphosphonium iodide, whereas the reaction occurred readily when the corresponding bromide was used as the starting material.[256]

Finally, it should be mentioned that alkylidene phosphoranes may react with t-butyl alcohol to form isobutylene by elimination of water.[91]

$$(C_6H_5)_3P=CCl_2 + (CH_3)_3COH \rightarrow (C_6H_5)_3PO + CH_2Cl_2 + (CH_3)_2C=CH_2$$

The use of t-butyl alcohol as a solvent for Wittig reactions should therefore be avoided.

THE SYNTHESIS OF NATURAL PRODUCTS

In no field has the Wittig reaction attained importance as rapidly as in the area of natural products chemistry. Three classes of compounds, especially, have become much more readily accessible. These are the naturally occurring polyacetylenic compounds; the carotenoids, including vitamin A; and methylene steroids and vitamin D. The Wittig reaction has also been applied to the synthesis of a number of other classes of natural products.

Polyacetylenic Compounds

In recent years it has been found that compounds containing conjugated double and triple bonds occur widely in plants. The synthesis of such unsaturated carbon chains was previously very difficult because no

[114] Collins and Hammond, J. Org. Chem., 25, 1434 (1960).

suitable method existed for the introduction of a double bond in a precisely defined position. It is therefore not surprising that the Wittig reaction found very early application in the synthesis of naturally occurring polyacetylenic compounds. Bohlmann and collaborators, especially, provided proof for the usefulness of the new method in this area.

The first step in the synthesis of oenanthetol (188), found in hemlock water dropwort (*Oenanthe crocata*) consisted of the preparation of dodeca-3,5-dien-1-yne (187) in 43% yield by means of a Wittig reaction.[257] Oxidative coupling of the hydrocarbon 187 with pent-2-en-4-yn-1-ol in the presence of cuprous chloride gave oenanthetol (188) in 14.1% yield in addition to the two symmetrical polyenynes.

$$n\text{-}C_6H_{13}CH=CHCH=P(C_6H_5)_3 \ + \ HC\equiv CCHO$$

$$\downarrow$$

$$n\text{-}C_6H_{13}CH=CHCH=CHC\equiv CH$$

187

$$\downarrow Cu_2Cl_2/O_2 + HC\equiv CCH=CHCH_2OH$$

$$n\text{-}C_6H_{13}(CH=CH)_2(C\equiv C)_2CH=CHCH_2OH$$

188
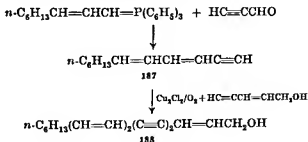
The same method was used for the synthesis of cicutol (190), isolated from European water hemlock (*Cicuta virosa*). Oxidative coupling of dodeca-3,5,7-trien-1-yne (189), obtained in 60% yield by a Wittig reaction, gave a mixture of three hydrocarbons from which cicutol (190) could be isolated by chromatography.[258] Small amounts of 10-*cis*-cicutol

$$n\text{-}C_4H_9CH=CHCH=P(C_6H_5)_3 \ + \ HC\equiv CCH=CHCHO$$

$$\downarrow$$

$$n\text{-}C_4H_9CH=CHCH=CHCH=CHC\equiv CH$$

189

$$\downarrow Cu_2Cl_2/O_2 + HC\equiv CCH_2CH_2CH_2OH$$

$$n\text{-}C_4H_9(CH=CH)_3(C\equiv C)_2CH_2CH_2CH_2OH$$

190
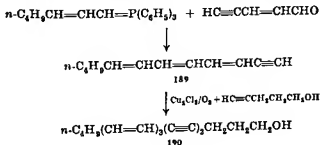
also formed were converted into the all-*trans* form with iodine in petroleum ether.

[257] Bohlmann and Viehe, *Chem. Ber.*, **88**, 1245 (1955).

[258] Bohlmann and Viehe, *Chem. Ber.*, **88**, 1347 (1955).

Trideca-1,3,5,11-tetraene-7,9-diyne (191), found in a number of coreopsis species, was synthesized by two different methods.[259] Path A

$$CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCH{=}P(C_6H_5)_3 \; + \; CH_2{=}CHCHO$$

$$\downarrow A$$

$$CH_3CH{=}CH(C{\equiv}C)_2(CH{=}CH)_2CH{=}CH_2$$
191

$$\uparrow B$$

$$CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCHO \; + \; (C_6H_5)_3P{=}CHCH{=}CH_2$$
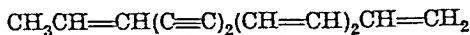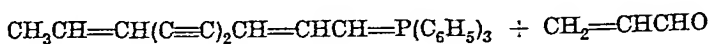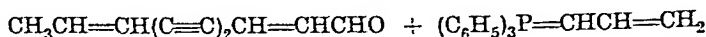
gave only poor yields as compared with about a 50% yield via path B.

The synthesis of aethusanol B (194), found in fool's-parsley (*Aethusa cynapium L.*), also started with a Wittig reaction.[260] Propargyl aldehyde and the phosphorane 192 furnished the intermediate 193 which with

$$CH_3CH_2CH{=}CHCH{=}P(C_6H_5)_3 \; + \; HC{\equiv}CCHO \rightarrow$$
192

$$CH_3CH_2CH{=}CHCH{=}CHC{\equiv}CH \xrightarrow{BrC{\equiv}CCH{=}CHCH_2OH}$$
193
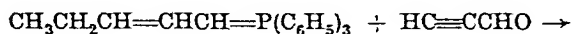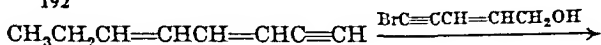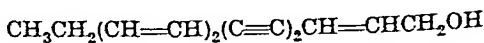
$$CH_3CH_2(CH{=}CH)_2(C{\equiv}C)_2CH{=}CHCH_2OH$$
194

5-bromopent-2-en-4-yn-1-ol gave aethusanol B (194), identical with one of the three *Aethusa* polyynes.

Hydroxyl groups may also be introduced in the initial stage of a synthesis by using a suitably substituted alkylidene phosphorane, as illustrated by the following two examples. The "chamomilla ester" 195 found in the German camomile (*Matricaria chamomilla L.*) and in *Matricaria discoidea DC.* was prepared by the following method.[71]

$$CH_3(C{\equiv}C)_2(CH{=}CH)_2CHO \; + \; (C_6H_5)_3P{=}CHCH_2CH_2O{-}\text{⬡}{\rightarrow}$$
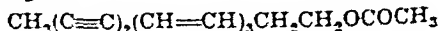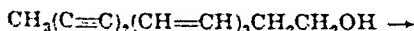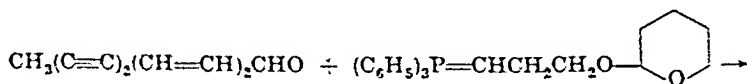
$$CH_3(C{\equiv}C)_2(CH{=}CH)_3CH_2CH_2OH \rightarrow$$
$$CH_3(C{\equiv}C)_2(CH{=}CH)_3CH_2CH_2OCOCH_3$$
195

Similarly, matricarianal (196) was converted to "centaur X$_2$" (197), the principal polyyne of the cornflower (*Centaurea cyanus L.*).[72]

[259] Bohlmann and Mannhardt, *Chem. Ber.*, 88, 1330 (1955).
[260] Bohlmann, Arndt, Bornowski, and Herbst, *Chem. Ber.*, 93, 981 (1960).

$$CH_3CH=CH(C\equiv C)_2CH=CHCHO + (C_6H_5)_3P=CHCH_2$$

196

1. Wittig
2. $H^\oplus/H_2O$
3. Acetylation

$$CH_3CH=CH(C\equiv C)_2(CH=CH)_2CH=CHCHCH_2CH_2OOCCH_3$$

$$|$$
$$OOCCH_3$$

197
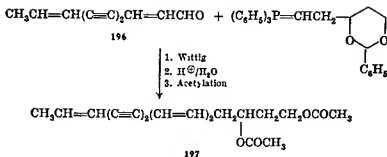
The polyyne hydrocarbons **198** and **199** were also synthesized by the Wittig reaction. The former is found in common mugwort (*Artemisia vulgaris*) and in the cornflower (*Centaurea cyanus L.*), the latter in a number of coreopsis species.[160,261]

$$CH_3(C\equiv C)_2(CH=CH)_4(CH_2)_4CH=CH_2 \qquad C_6H_5(C\equiv C)_2(CH=CH)_2CH_2$$

198   **199**
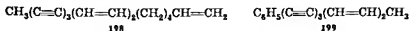
Carotenoids and Vitamin A

The synthesis of carotenoids and vitamin A using the Wittig reaction has received particular attention.[262,263] The synthesis of unsymmetrical carotenoids such as α- and γ-carotene is best carried out using only two components, a polyene aldehyde and an alkylidene phosphorane. Thus γ-carotene (**200**) can be prepared according to the scheme $C_{30} + C_{10} = C_{40}$.[264]

200
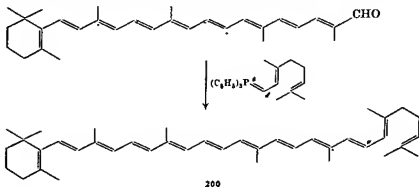
Another possibility is the combination of a C_{25}-aldehyde with a C_{15}-phosphorane according to the scheme $C_{25} + C_{15} = C_{40}$. Often the

[261] Bohlmann, *Chem. Ber.*, **88**, 1755 (1955).
[262] Pommer, *Angew. Chem.*, **72**, 811 (1960).
[263] Pommer, *Angew. Chem.*, **72**, 911 (1960).
[264] Rüegg, Schwieter, Ryser, Schudel, and Isler, *Helv. Chim. Acta*, **44**, 985 (1961).

15,15'-dehydro derivative is prepared first, then partially hydrogenated and isomerized to the all-*trans*-γ-carotene (200).[254]
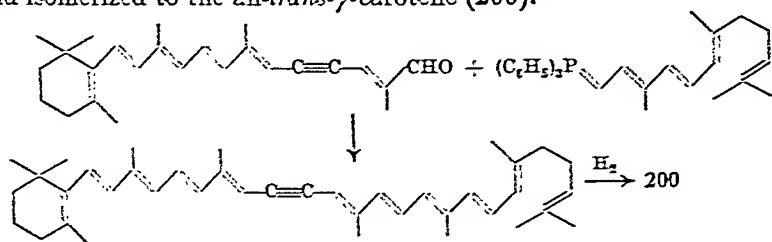
7',8'-Dihydro-γ-carotene (β-zeacarotene), found in corn, was synthesized by the same method.[255]   3',4'-Dehydro-γ-carotene (torulin, 201), isolated from *Torula rubra*, on the other hand, was prepared according to the scheme $C_{35} + C_5 = C_{40}$.[255]

201
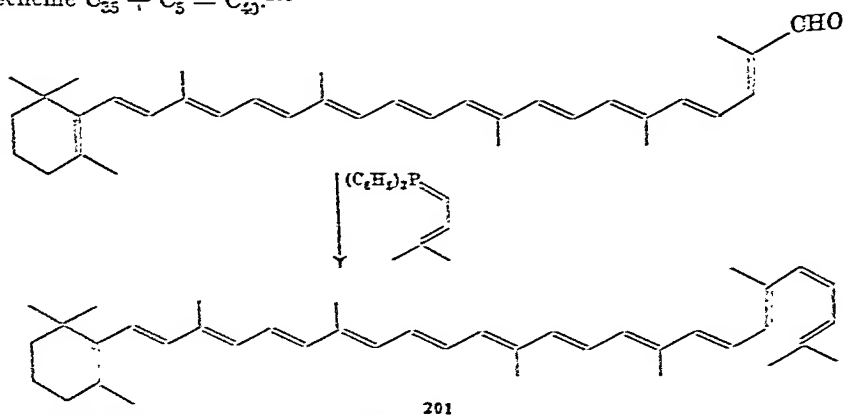
The synthesis of α-carotene (202) followed the scheme $C_{25} + C_{15} = C_{40}$.[254]

202
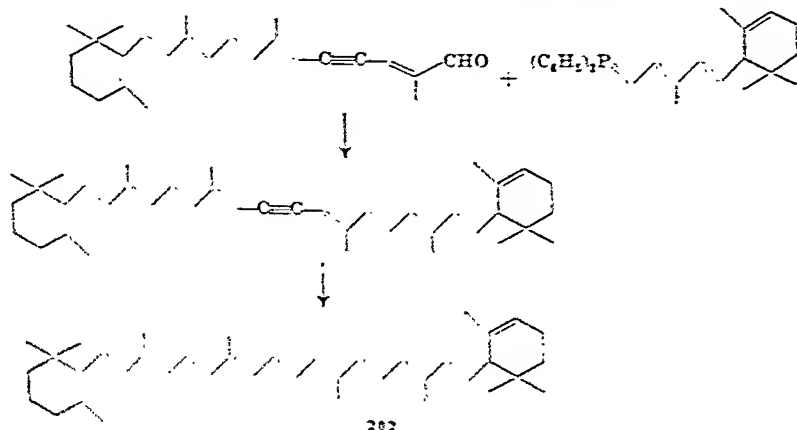
Symmetrical carotenoids such as β-carotene and lycopene may, of
course, be prepared by the same method.[264] β-Carotene (44) has also
been obtained by the scheme $C_{20} + C_{20} = C_{40}$, starting from vitamin A
aldehyde (203).[266]
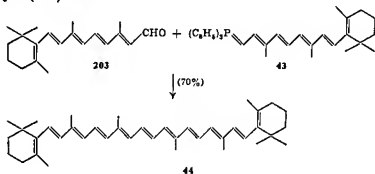
In place of axerophthylenetriphenylphosphorane (43), the isomeric ylide
204, which is in equilibrium with 43, may also be used.[267]
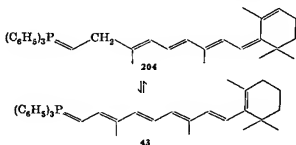
The synthesis of symmetrical carotenoids, however, is better carried
out by the interaction of dialdehydes with 2 moles of an alkylidene
phosphorane or of a bifunctional ylide with 2 moles of an aldehyde.
Thus β-carotene (44) is obtained in good yield according to the scheme
$C_{15} + C_{10} + C_{15} = C_{40}$ by either path A[54,268-270] or path B[80,271] (equations
on p. 360). Using path B but starting from vitamin A aldehyde,
decapreno-β-carotene is obtained in 38 % yield.[80,271]

The scheme $C_{13} + C_{14} + C_{13} = C_{40}$ illustrates another possible com-
bination.[209,260,272] In each case, mixtures of the cis and trans isomers are

[265] Pommer and Sarnecki, Ger. pat. 1,068,709 (to BASF) [C.A., 55, 13472; (1961)].
[267] Stern, U.S. pat. 2,945,069 (to Eastman Kodak) [C.A., 55, 608e (1961)].
[268] Pommer and Sarnecki, Ger. pat. 1,068,705 (to BASF) [C.A., 55, 13473i (1961)].
[269] Pommer and Sarnecki, Ger. pat. 1,068,705 (to BASF) [C.A., 56, 1487f (1962)].
[270] Pommer and Sarnecki, Ger. pat. 1,068,710 (to BASF) [C.A., 55, 12446g (1961)].
[271] Surmatis, Ger. pat. 1,105,869 (to Hoffmann LaRoche), 1959.
[272] Pommer and Sarnecki, Ger. pat. 1,068,704 (to BASF) [C.A., 55, 13473f (1961)].
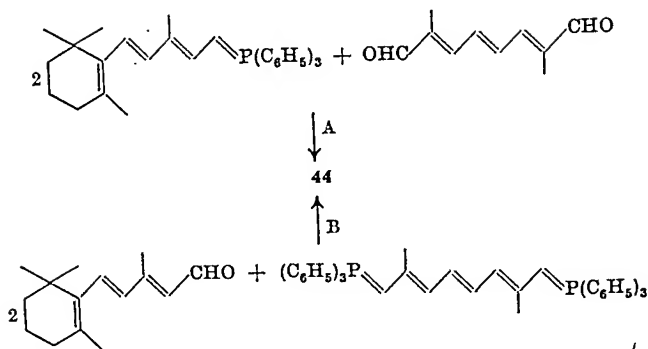
obtained. The mixtures can be converted to the all-*trans* form by heating with iodine. The isomerization to the all-*trans* compound can also be effected by nitric oxide.[272]
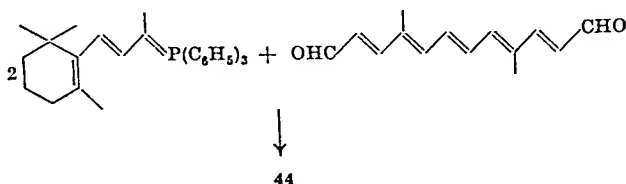
Another possibility for the synthesis of symmetrical carotenoids is expressed by the scheme $C_{10} + C_{20} + C_{10} = C_{40}$. β-Carotene (44) can thus be obtained from crocetin dialdehyde (206) and 2 moles of β-cyclo-geranylidenetriphenylphosphorane (205).[273,274] Good yields were obtained only by using dimethylformamide as the solvent.[274]
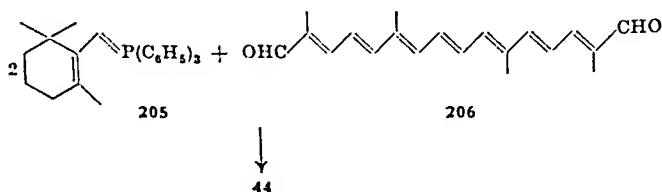
By the same method, lycopene (208), the pigment of the tomato, was prepared starting from geranylidenetriphenylphosphorane (207).[274–277]

[272] Isler, Montavon, Rüegg, and Zeller, Ger. pat. 1,017,165 (to Hoffmann-LaRoche) [*C.A.*, 53, 18982b (1959)].

[274] Pommer and Sarnecki, Ger. pat. 1,068,707 (to BASF) [*C.A.*, 55, 10499a (1961)].

[275] Isler, Gutmann, Lindlar, Montavon, Rüegg, Ryser, and Zeller, *Helv. Chim. Acta*, 39, 463 (1956).

[276] Isler, Montavon, Rüegg, and Zeller, Ger. pat. 1,038,033 (to Hoffmann-LaRoche) [*C.A.*, 54, 17456h (1960)].

[277] Isler, Montavon, Ruegg, and Zeller, U.S. pat. 2,842,599 (to Hoffmann-LaRoche) [*C.A.*, 53, 2279h (1959)].

207 + **206**

↓

208
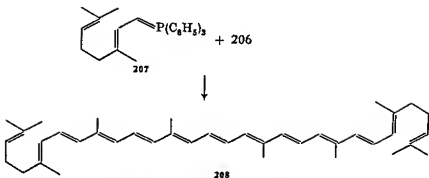
Spirilloxanthene,[278] dehydrolycopene, and 1,1'-dihydroxy-1,2,1',2'-tetrahydrolycopene[279] were synthesized by essentially the same method.

All these possible synthetic routes may, of course, be applied to the preparation of 15,15'-dehydrocarotenoids. Partial hydrogenation of these compounds leads to the 15,15'-*cis*-carotenoids, which are converted to the all-*trans*-carotenoids on recrystallization or heating in an inert solvent.[290]

The synthesis of vitamin A and its derivatives is carried out by starting from monofunctional carbonyl compounds and ylides. Vitamin A methyl ether (**209**) is thus obtained according to the scheme $C_{18} + C_2 = C_{20}$.[281]

$+ (C_6H_5)_3P=CHCH_2OCH_3$

209
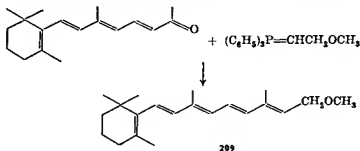
The low yield, 10%, is probably due to the instability of the ylide **210**.[133]

$$(C_6H_5)_3P=CH-CH_2-OCH_3 \rightarrow (C_6H_5)_3\overset{+}{P}-CH=CH_2 + CH_3\overset{-}{O}$$

210
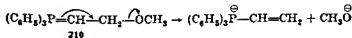
The vitamin A skeleton may be obtained by generating any one of the four double bonds in the side chain by combination of suitable aldehydes

[278] Surmatis and Ofner, 142nd Meeting, Am. Chem. Soc., Atlantic City, N.J., Sept. 1962, Abstracts, p. 48Q.

[279] Surmatis and Ofner, 142nd Meeting, Am. Chem Soc., Atlantic City, N.J., Sept 1962, Abstracts, p. 50Q.

[280] Brit. pat. 793,236 (to Hoffmann-LaRoche) [*C.A.*, 54, 627g (1960)].

[281] Isler, Montavon, Rüegg, and Zeller, Ger. pat. 1,017,163 (to Hoffmann-LaRoche) [*C.A.*, 53, 15982c (1959)].

and phosphoranes. The vitamin A acid methyl ester (212a), for example, was prepared from β-ionylideneacetaldehyde (211) according to the scheme $C_{15} + C_5 = C_{20}$.[55,282]

211
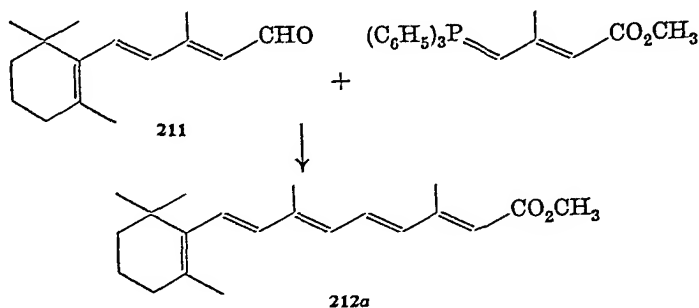
212a

Better yields are obtained by the reaction between the phosphorane 213 and β-formylcrotonic ester (214).[270,283-286]

213

214

212
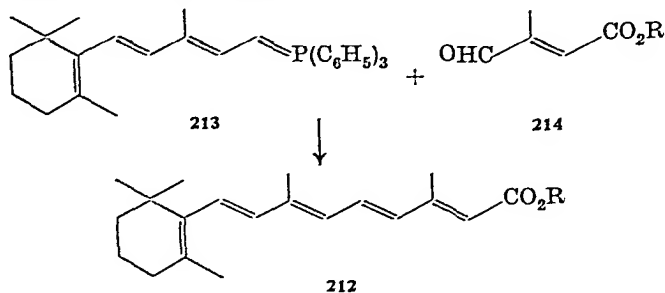
The esters of vitamin A acid (212) are readily saponified to vitamin A acid (216). The latter can be obtained directly from β-formylcrotonic acid (215) and the ylide 213, provided that the free acid is converted to its salt by excess alkali.[270,284-286]

213

215
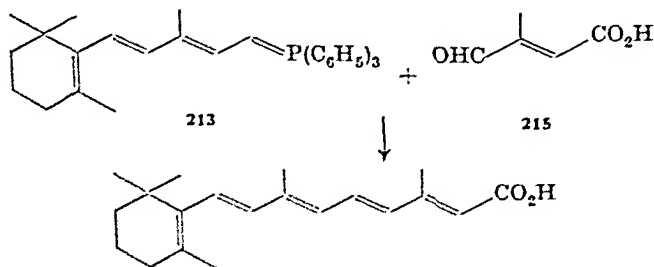
The same scheme was used to synthesize vitamin A acetate (217),[270,284,285] vitamin A methyl ether (209),[256a] and desoxy vitamin A or axerophthene (218).[270,284,285,287]

217

218
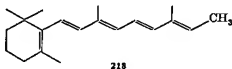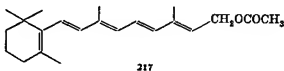
The synthesis of vitamin A_2 and its derivatives according to the scheme $C_{15} + C_5 = C_{20}$ is illustrated by the preparation of vitamin A_2 acid methyl ester (219).[241]

219 (90%)
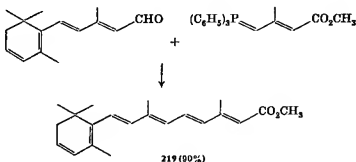
Analogously, the vitamin A_2 carbonitrile is obtained in 86% yield. Conversely, β-formylcrotonic ester (214) may also be used as the starting material. The ester of vitamin A_2 acid may subsequently be reduced to vitamin A_2 (220) with lithium aluminum hydride.[288]

220
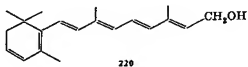
[285a] Isler, Montavon, Ruegg, and Zeller, Ger. pat. 1,017,164 (to Hoffmann-La Roche) [C.A., 53, 18982d (1959)].

[287] Pommer and Wittig, Ger. pat. 1,029,366 (to BASF) [C.A., 54, 22713h (1960)].

[288] Schwieter, Planta, Rüegg, and Isler, Helv. Chim. Acta, 45, 541 (1962).

The synthesis of the vitamin A skeleton according to the scheme $C_{13} + C_7 = C_{20}$ is illustrated · by two syntheses of axerophthene (218).[209,240,287,289]
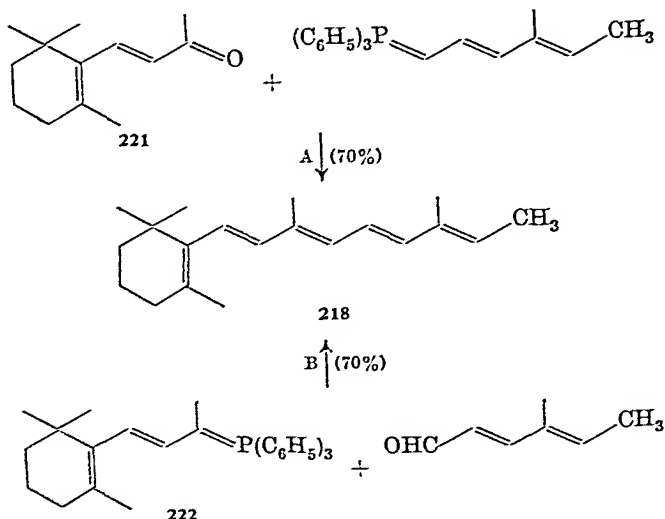
Path A, which starts with β-ionone (221), was also used for the preparation of vitamin A methyl ether (209) and of vitamin A acetate (217).[290] Vitamin A acid (216)[291,292] and its ethyl ester (212b)[259,292] were obtained in excellent yields via path B starting from β-ionylidenetriphenylphosphorane (222).

Finally, it may be mentioned that vitamin A acid ethyl ester (212b) was prepared from β-cyclogeranylidenetriphenylphosphorane (223) according to scheme $C_{10} + C_{10} = C_{20}$.[293] Analogously, axerophthene (218) was prepared in 60% yield.[293]
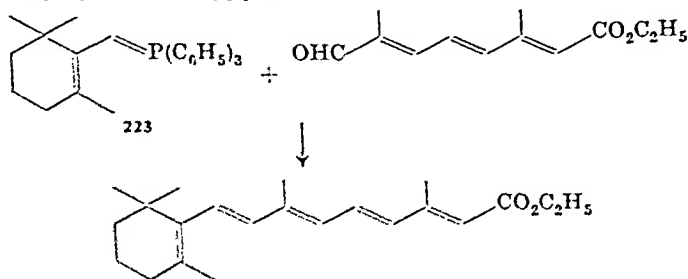
Higher homologs (224; $n = 2, 3$) of vitamin A acid and carotene acids of the form 225 and 226 ($n = 0, 1, 2, 3$) have also been synthesized by means of the Wittig reaction.

224

225

226
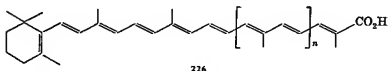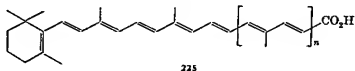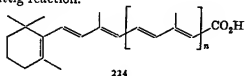
Homoisoprenovitamin A acid (224; $n = 2$), for instance, was prepared by four different methods.[240,266,269,270,294]
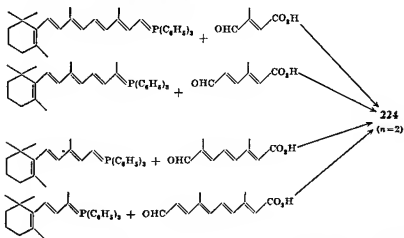
Of the many syntheses of polyenecarboxylic acids (225 and 226),[295–298] mention is made only of the preparation of torularhodin (226; $n = 3$),

[294] Pommer and Sarnecki, Ger. pat. 1,070,173 (to BASF) [C.A., 55, 11332h (1961)].

[295] Isler, Guex, Rüegg, Ryser, Saucy, Schwieter, Walter, and Winterstein, Helv. Chim. Acta, 42, 864 (1959).

[296] Rüegg, Guex, Montavon, Schwieter, Saucy, and Isler, Angew. Chem., 71, 80 (1959).

[297] Guex, Rüegg, Isler, and Ryser, Ger. pat. 1,088,951 (to Hoffmann-La Roche), 1959; corresponds to Brit. pat. 850,137 [C.A., 55, 17541e (1961)].

[298] Guex, Isler, Rüegg, and Ryser, Ger. pat. 1,096,349 (to Hoffmann-La Roche), 1959; corresponds to Brit. pat. 875,713 [C.A., 56, 7372b (1962)].
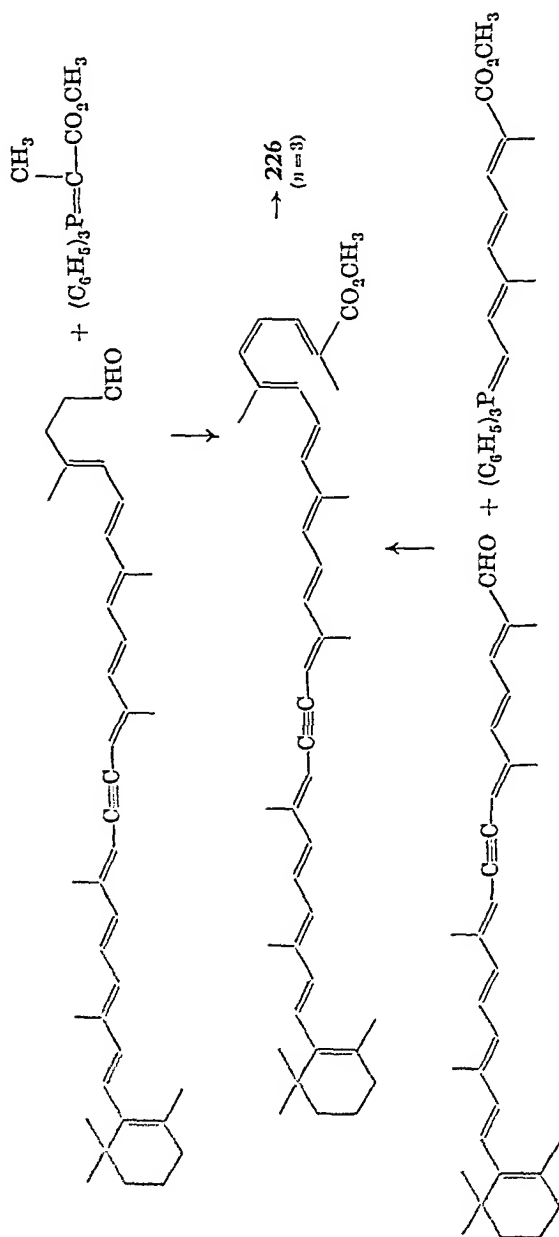
which definitely established the structure of the acid pigment of near yeast (*Torula rubra*).[295-297] (See p. 366.)

Diesters of norbixin such as methylbixin (228) have been prepared from crocetin dialdehyde (227) and carbalkoxymethylene triphenylphosphoranes according to the scheme $C_2 + C_{20} + C_2 = C_{24}$.[39.231] Methylbixin can

227

$+ 2(C_6H_5)_3P=CHCO_2CH_3$

228 (80%)
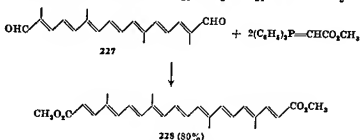
also be prepared in 76% yield by the scheme $C_5 + C_{14} + C_5 = C_{24}$.[233.234]

$+ 2(C_6H_5)_3P \underset{CO_2CH_3}{\underset{|}{}} \rightarrow 228$
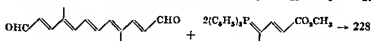
Crocin, the yellow pigment of saffron, is the digentiobiose ester of the C_{20}-dicarboxylic acid crocetin. Diesters of crocetin, such as crocetin dimethyl ester (229), can be synthesized by the same methods as those used for the preparation of norbixin, either according to scheme $C_2 + C_{16} + C_2 = C_{20}$[39.231] or $C_5 + C_{10} + C_5 = C_{20}$.[232.235]

$+ 2(C_6H_5)_3P \underset{CO_2CH_3}{\underset{|}{}}$

229

(84%)

$+ 2(C_6H_5)_3P \underset{CO_2CH_3}{\underset{|}{}}$
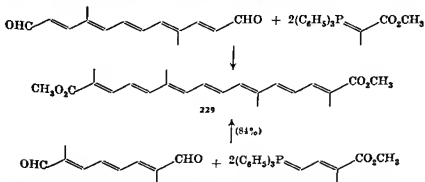
Finally, mention should be made of the synthesis of squalene, a triterpene related to the carotenoids, which is important as an intermediate in the biosynthesis of steroids. Squalene (232) was synthesized by the reaction of geranylacetone (230) with the bis-ylide 231 according to scheme $C_{13} + C_4 + C_{13} = C_{30}$.[74.299-301]

[299] Trippett, *Chem. Ind.* (*London*), 1956, 80.
[300] Dicker and Whiting, *Chem. Ind.* (*London*), 1956, 351.
[301] Dicker and Whiting, *J. Chem. Soc.*, 1958, 1994.

230 + $(C_6H_5)_3P$=$\overset{*}{C}HCH_2CH_2\overset{*}{C}H$=$P(C_6H_5)_3$ **231**

232
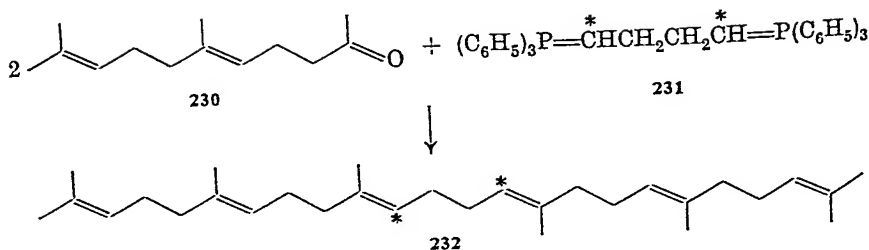
The all-*trans*-squalene (**232**) was isolated in 12% yield from the mixture of *cis* and *trans* isomers by way of the thiourea clathrate.[300,301] Analogously, radioactively labeled squalene (^{14}C-labeled at C_{11} and C_{14}) was prepared in 50% yield from the ^{14}C-labeled bis-ylide **231**.[302]

Steroids and Vitamin D

The method of introducing exocyclic double bonds by means of the Wittig reaction has been used in steroid chemistry. The preparation of 3-methylenecholestane (**234**) from cholestan-3-one (**233**) and methylene-triphenylphosphorane was the first instance of a conversion of a steroid ketone to a methylenesteroid by this method.[303] This synthesis was

233 + $(C_6H_5)_3P$=CH_2 → **234**
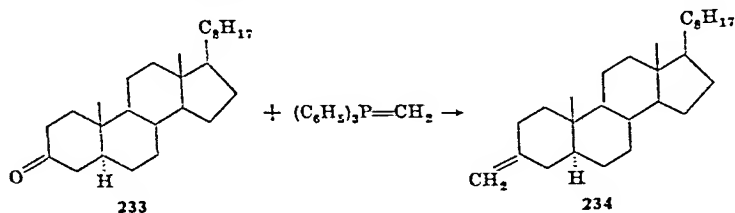
followed by the preparation of a whole series of methylenesteroids in similar fashion, in the course of which it was found that excess methylene-triphenylphosphorane increased the yields.[254] 17-Methyleneandrostan-3β-ol (**236**) was obtained in 58% yield from androstan-3β-ol-17-one (**235**) by using a five-fold excess of methylenephosphorane, but in only 32% yield by employing 3 moles of ylide.[254] The yield in this reaction was

235 + $5(C_6H_5)_3P$=CH_2 → **236**
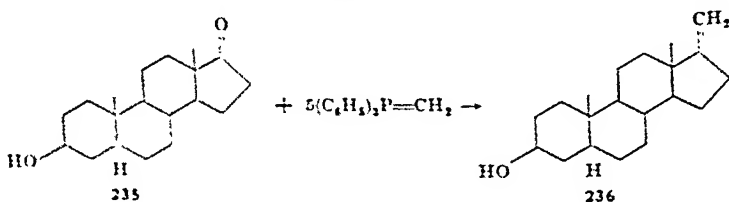
also increased when the 3-hydroxyl group was blocked by conversion to the tetrahydropyranyl ether. The increased yield, however, was offset by losses in the formation and cleavage of the ether.

α,β-Unsaturated steroid ketones have also been used as starting materials. Δ⁴-Cholesten-3-one (237), for instance, gives 3-methylene-Δ⁴-cholestene (238) in 80% yield.[254]
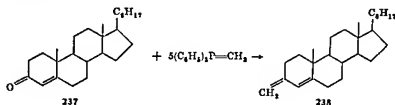
Acetate esters are cleaved by ylides, as illustrated by the preparation of 7-methylenecholesterol (240) from 7-ketocholesteryl acetate (239).[254]
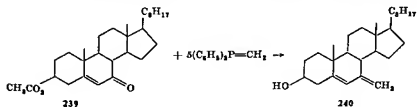
The use of methoxymethylenetriphenylphosphorane in place of methylenetriphenylphosphorane in these syntheses leads to exocyclic enol ethers that can be saponified to the corresponding formyl compounds. An example is the synthesis of 3-formyl-5α,22β,25D-spirostane (242) from tigogenone (241)[246]
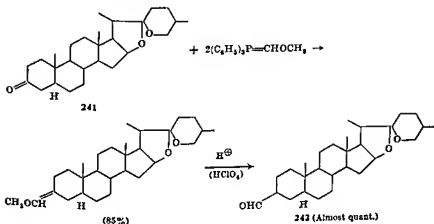
Monomethylene compounds can be isolated from some steroid diketones. The 3-keto group in androstane-3,7-dione (243) is the more reactive, and 3-methyleneandrostan-17-one (244) can be obtained. Further action of methylenetriphenylphosphorane forms 3,17-dimethyleneandrostane (245).[252]

243   244 (55%)   245 (76%)
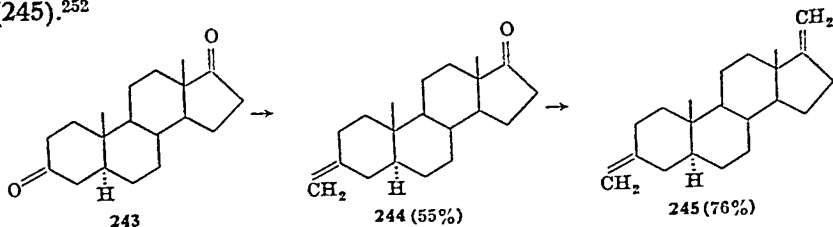
Steroid diketones containing keto groups of comparable reactivities give the dimethylene compounds directly, as illustrated by the formation of 3,20-dimethyleneallopregnane (247) in 75% yield from allopregnane-3,20-dione (246).[252]

246   247
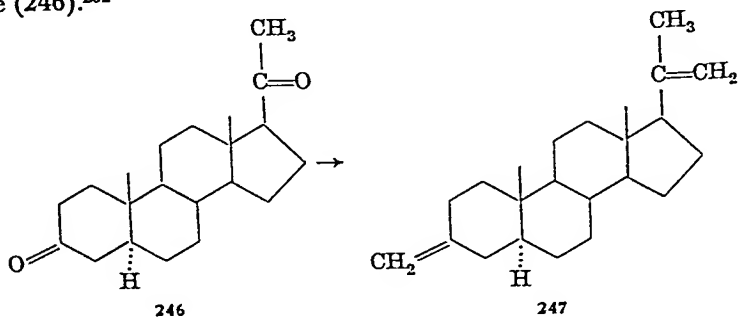
The same method has been used frequently to introduce a methylene group into the side chain of steroids. 24-Ketocholesteryl acetate (248) was converted in 70% yield to 24-methylenecholesterol (249)[301.304a] which proved to be identical with chalinasterol isolated from sponges and sea anemones, *Zoanthus proteus*, whose structure had been in dispute.[301]

248   249
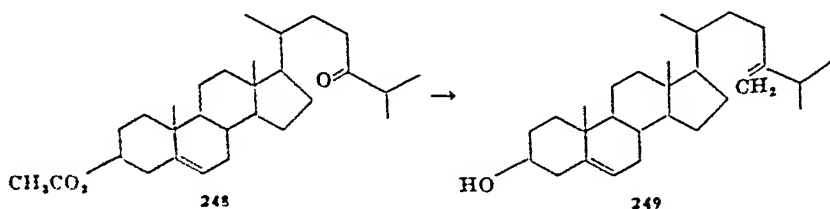
24-Dehydrocholesterol (251), isolated from acorn barnacle (*Balanus glandula*), was synthesized from 3β-acetoxy-5-cholenaldehyde (250).[305]

CH₃CO₂ ... 3β-acetoxy structure **250**

$+ (C_6H_5)_3P=C(CH_3)_2 \rightarrow$

HO ... **251**
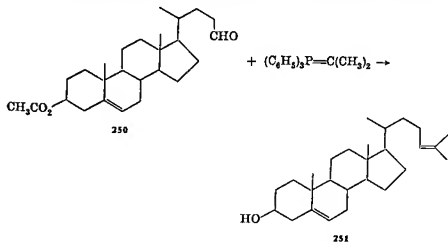
Similarly, 29-isofucosterol (252) was obtained from 24-ketocholesteryl acetate or 24-ketocholesteryl tetrahydropyranyl ether (248).[306,307]

RO ... **248**

$(C_6H_5)_3P=CHCH_3 \rightarrow$

HO ... **252**
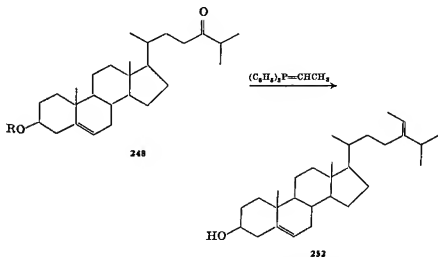
The usefulness of the Wittig reaction for the synthesis of vitamin D was tested first in the preparation of model trienes. The ketone 253

[305] Fagerlund and Idler, *J. Am. Chem. Soc.*, 79, 6473 (1957)

[306] Dusza, *J. Org. Chem.*, 25, 93 (1960)

[307] Fagerlund and Idler, *J. Fisheries Res. Board Can.*, 17, 597 (1960) [*C.A.*, 55, 2730h (1961)].

could be converted to the triene 254 which contains a double bond system typical of calciferol.[308,309]
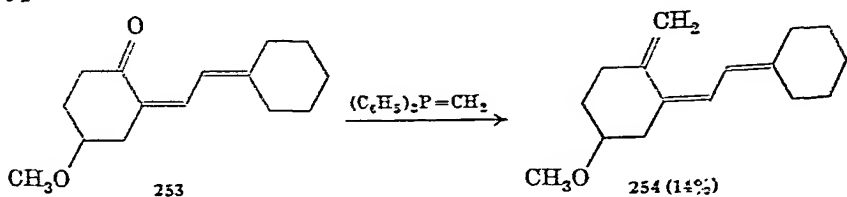
The unsubstituted model substance 256 was prepared analogously from the cyclohexanone derivative 255.[69,153,154,310,311]
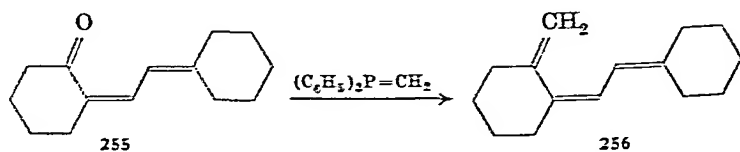
A biologically active homolog of vitamin D_2, 257, whose activity almost reached that of calciferol, was synthesized by the following route.[312]
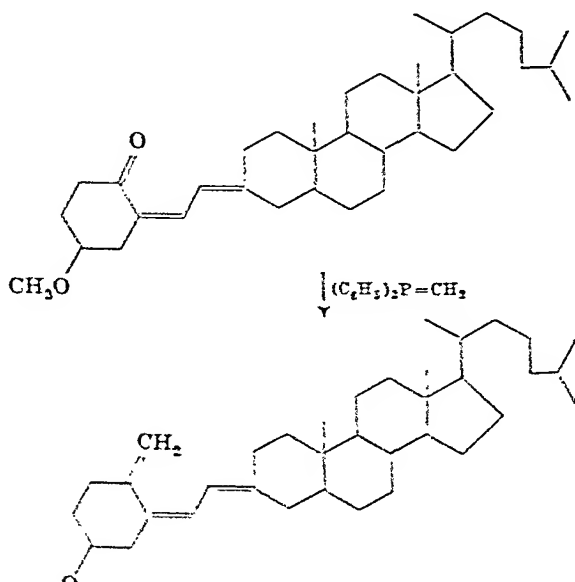
vitamins D_2 (calciferol) and D_3, which involved the use of the Wittig reaction in three of the steps.[70,158,313-321] The final steps of the synthesis are shown in the accompanying formulation. It is interesting to note that
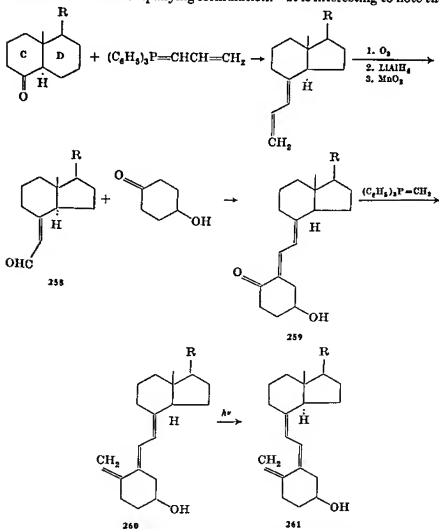
$$\text{(Vitamin } D_2: R = C_9H_{17}, = -CH(CH_3)CH=CHCH(CH_3)CH(CH_3)_2;}$$
$$\text{Vitamin } D_3: R = C_8H_{17}, = -CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2)}$$

[313] Inhoffen, Kath, and Bruckner, *Angew. Chem.*, **67**, 276 (1955)
[314] Inhoffen and Irmscher, *Chem. Ber.*, **89**, 1833 (1956).
[315] Inhoffen, Quinkert, and Hess, *Naturwiss*, **44**, 11 (1957).
[316] Inhoffen, Kath, Stscherling, and Bruckner, *Ann.*, **603**, 25 (1957).
[317] Inhoffen, Quinkert, Schutz, Kampe, and Domagk, *Chem. Ber.*, **90**, 664 (1957).
[318] Inhoffen, Quinkert, and Schütz, *Chem. Ber.*, **90**, 1283 (1957).
[319] Inhoffen, Irmscher, Hirschfeld, Stache, and Kreutzer, *Chem. Ber.*, **91**, 2309 (1958).
[320] Inhoffen, Burkhardt, and Quinkert, *Chem. Ber.*, **92**, 1564 (1959).
[321] Inhoffen, Irmscher, Friedrich, Kampe, and Berges, *Chem. Ber.*, **92**, 1772 (1959).

in the first step the *trans* configuration of the CD ring system is preserved. The condensation of the aldehyde **258** with *p*-hydroxycyclohexanone gives a mixture of epimers **259** from which the 3β-isomer could be isolated by chromatography. The 3β-5,6-*trans*-vitamin D (**260**) is then converted to vitamins D_2 and D_3 (**261**), respectively, by photoisomerization.

A mixture of calciferol (**261**) and epi-calciferol (**263**) was also obtained by a similar method.[310,311] The photoisomerization, however, was carried out with the ketone **259**, and the mixture of epimers **262** so obtained was subjected to the Wittig reaction.

259   262

261   263

$(R = C_9H_{17})$
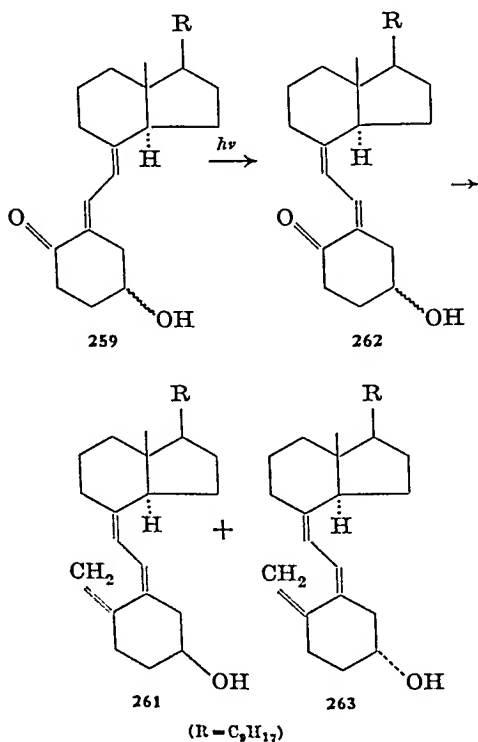
Other Natural Products

The Wittig reaction has also been instrumental in the synthesis of a number of other natural products that do not belong to any of the three groups discussed above. Again, the possibility of introducing exocyclic double bonds by means of methylenetriphenylphosphorane is of decisive importance in these syntheses. The alkaloid 1-methylenepyrrolizidine

(265), for example, can be synthesized in 63% yield from 1-pyrrolizidone (264).[322]

$$+ \ (C_6H_5)_3P=CH_2 \ \rightarrow$$
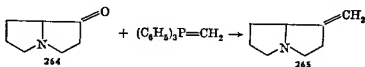
In many cases the exocyclic double bond is subsequently hydrogenated catalytically, so that the over-all effect is the transformation

$$\begin{array}{c} \diagdown \\ \diagup \end{array} C=O \ \rightarrow \ \begin{array}{c} \diagdown \\ \diagup \end{array} CHCH_3$$
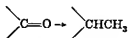
Thus 6-methyldihydrodesoxycodeine (268) was prepared from dihydrocodeinone (266) by way of 6-methylenedihydrodesoxycodeine (267).[175]
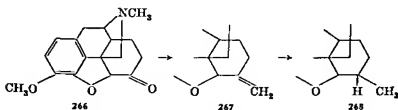
Similarly β-patchoulene (270) was synthesized in 38% over-all yield from the ketone 269.[176]
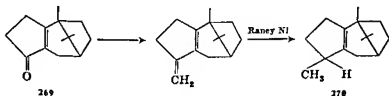
The selective reduction of an exocyclic double bond can also be done with lithium in diethylamine, as illustrated by the synthesis of α-amyrin from glycyrrhetic acid, a β-amyrin derivative of known configuration, which elucidated the structure and configuration of that triterpene.[323]

Dihydrotremetone (273) was synthesized from 2-acetylbenzofuran (271) via 2-isopropenylbenzofuran (272).[324]

[322] Kochetkov, Likhosherstov, and Kritsyn, *Tetrahedron Letters*, 1961, 92.
[323] Corey and Cantrall, *J. Am. Chem. Soc.*, **80**, 499 (1958).
[324] DeGraw and Bonner, *Tetrahedron*, **18**, 1311 (1962).
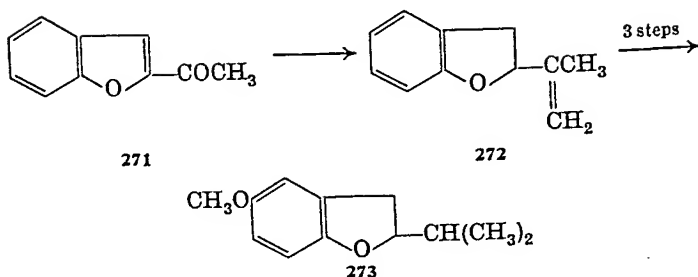
The royal jelly of the honey bee, an α,β-unsaturated acid of structure **276**, was synthesized from glutaraldehyde (**274**).[228,229] The intermediate 6-(methoxycarbonyl)-5-hexenal (**275**) was converted to 9-oxo-2-decenoic acid (**276**) in four steps. The *trans* isomer (royal jelly) could be isolated in a total yield of 12–15%.

$$OHC(CH_2)_3CHO \; + \; (C_6H_5)_3P{=}CHCO_2CH_3 \longrightarrow$$
$$\underset{\textbf{274}}{}$$

$$\underset{\textbf{275 (83\%)}}{OHC(CH_2)_3CH{=}CHCO_2CH_3} \xrightarrow{\text{4 steps}}$$

$$\underset{\textbf{276}}{CH_3CO(CH_2)_5CH{=}CHCO_2H}$$
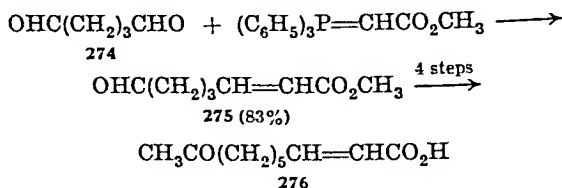
Finally, the important syntheses of insect sex attractants should be mentioned.[161,325–327] Bombycol, the sex attractant of the female silk moth (*Bombyx mori L.*), was found to be hexadeca-*trans*-10,*cis*-12-dien-1-ol (**280**). All possible *cis-trans* isomers of the hexadecadienol were prepared by different routes using the Wittig reaction. Bombycol itself was synthesized from 9-(ethoxycarbonyl)nonanal (**277**) and the ylide **278** according to the scheme $C_{10} + C_6 = C_{16}$.[325] The *trans* ester was isolated

$$C_2H_5O_2C(CH_2)_8CHO \; + \; (C_6H_5)_3P{=}CHC{\equiv}C(CH_2)_2CH_3 \xrightarrow{46\%}$$
$$\underset{\textbf{277}}{} \qquad\qquad \underset{\textbf{278}}{}$$

$$\underset{\textbf{279}}{C_2H_5O_2C(CH_2)_8CH{=}CHC{\equiv}C(CH_2)_2CH_3} \longrightarrow$$
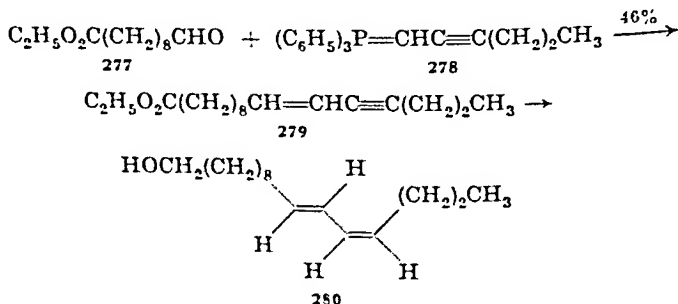
from the mixture of *cis* and *trans* isomers 279 by means of its urea clathrate and converted to bombycol (280) by partial hydrogenation followed by lithium aluminum hydride reduction.

An alternative route to bombycol (280) from 9-(methoxycarbonyl)-nonanal (277a) that involves two Wittig reactions is shown in the accompanying formulations.[161,326,327]

$$CH_2O_2C(CH_2)_6CHO + (C_6H_5)_3P=CHCOCH_3 \xrightarrow{67\%}$$
$$\underset{277a}{}$$

$$CH_2O_2C(CH_2)_6 \quad\underset{CO_2CH_3}{\overset{H}{\diagup}} \longrightarrow HOCH_2(CH_2)_6 \quad\underset{CHO}{\overset{H}{\diagup}} \longrightarrow$$

$$CH_3CO_2CH_2(CH_2)_8 \quad\underset{CHO}{\overset{H}{\diagup}} + (C_6H_5)_3P=CH(CH_2)_2CH_3 \xrightarrow{71\%}$$

$$CH_3CO_2CH_2(CH_2)_8 \quad\underset{H}{\overset{H}{\diagup}}\quad\underset{H}{\overset{(CH_2)_2CH_3}{\diagup}} \xrightarrow{OH^\ominus}$$

$$HOCH_2(CH_2)_8 \quad\underset{H}{\overset{H}{\diagup}}\quad\underset{H}{\overset{(CH_2)_2CH_3}{\diagup}}$$
$$\underset{280}{}$$
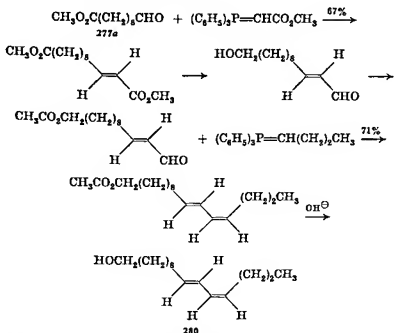
By similar methods, the remaining hexadeca-10,12-dien-1-ols,[161,325–327] as well as other unsaturated aliphatic alcohols, have been synthesized.[327,328]

The elegant syntheses of oleic acid and other naturally occurring unsaturated fatty acids containing *cis* double bonds have been mentioned previously.[114]

MODIFIED PROCEDURES AND RELATED REACTIONS

The pyrolysis of β-ketoalkylidene triphenylphosphoranes under certain conditions gives acetylenes by an intramolecular Wittig reaction.[41,329–331] The reaction is successful only if neither R_1 nor R_2 is

[325] Truscheit and Eiter, Austrian pat. 220,133 (to Farbenf. Bayer), 1960.
[326] Gough and Trippett, *Proc. Chem. Soc.*, 1961, 302.
[327] Gough and Trippett, *J. Chem. Soc.*, 1962, 2333.
[328] Märkl, *Chem. Ber.*, 94, 3005 (1961)

hydrogen. In addition, R_1 or R_2 must be a substituent capable of resonance, such as a phenyl, ester, or nitrile group. If these conditions are

$$(C_6H_5)_3P \overset{R_1}{\underset{\underset{O}{\overset{|}{C}}\overset{R_2}{}}{\overset{|}{C}}} \longrightarrow (C_6H_5)_3\overset{\ominus}{P} \overset{R_1}{\underset{\underset{\ominus O}{\overset{||}{C}}\overset{R_2}{}}{\overset{|}{C}}} \xrightarrow{280°} (C_6H_5)_3PO + R_1C{\equiv}CR_2$$
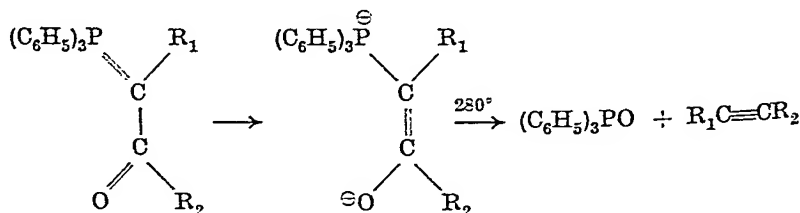
met, acetylenic compounds are obtained in excellent yields. Thus acetylcarbethoxymethylenetriphenylphosphorane (281) could be converted to ethyl 2-butynoate (282) in 91 % yield.[329]

$$(C_6H_5)_3\overset{\ominus}{P} \overset{CO_2C_2H_5}{\underset{\underset{\ominus O}{\overset{||}{C}}\overset{CH_3}{}}{\overset{|}{C}}} \xrightarrow{280°/10\ mm.} CH_3C{\equiv}CCO_2C_2H_5$$

281   282
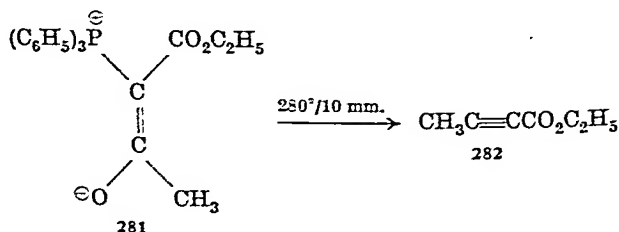
A large number of α,β-acetylenecarboxylic esters has been synthesized in this manner.[231] In analogous fashion phenylpropiolonitrile is formed by pyrolysis of the phosphorane 283.[329]

$$(C_6H_5)_3\overset{\ominus}{P} \overset{CN}{\underset{\underset{\ominus O}{\overset{||}{C}}\overset{C_6H_5}{}}{\overset{|}{C}}} \longrightarrow C_6H_5C{\equiv}CCN$$

                               (85%)

283
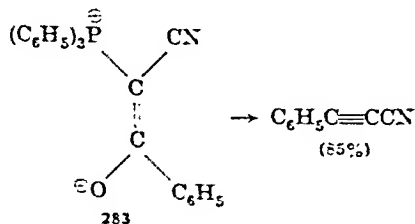
In recent years, practical and theoretical considerations have frequently led to modifications of the Wittig reagents, either by substituting the phenyl groups on phosphorus by other substituents or by replacing the phosphorus by other central atoms.

The use of phosphoranes containing basic substituents such as the acetylmethylene-p-dimethylaminophenyldiphenylphosphorane (284) is recommended because the corresponding phosphine oxide can be readily

separated from the other reaction products by extraction of the ether solution with dilute acid.[192]

$$p\text{-}(CH_3)_2NC_6H_4\overset{}{P}(C_6H_5)=CHCOCH_3 \ + \ C_6H_5CHO \xrightarrow{78\%}$$
$$\underset{284}{\underset{O}{\|}}$$

$$p\text{-}(CH_3)_2NC_6H_4\overset{O}{\underset{\|}{P}}(C_6H_5)_2 \ + \ C_6H_5CH=CHCOCH_3$$
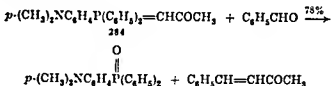
Replacement of the phenyl groups on phosphorus by electron-releasing substituents will result in decreased yields in reactions of normal ylides which are not resonance-stabilized. As discussed previously, the second step of the Wittig reaction, decomposition of the betaine, is rate-determining in these cases, and increased electron density on the phosphorus will have an unfavorable effect. For example, the high yields which can be obtained with methylenetriphenylphosphorane could, in no case, be duplicated with the methylene phosphoranes 66a–f (see p. 311).[155]

Aliphatic substituents on phosphorus, such as methyl[102] or cyclohexyl groups,[29] also decrease the yields. The situation is different for the resonance-stabilized phosphoranes of the second group, for which the first step of the Wittig reaction is rate-determining. Electron-releasing groups on phosphorus have a favorable effect because they increase the nucleophilicity of the ylides. Thus fluorenylidenetri-n-butylphosphorane always gives better yields with aldehydes and ketones than does fluorenylidenetriphenylphosphorane.[29] Increased reactivity has been observed also in other resonance-stabilized phosphoranes in which the phenyl groups on phosphorus had been replaced by alkyl groups.[29,58,212,222] In addition, alkyl groups on phosphorus influence the stereochemistry of the Wittig reaction, the trans isomers being formed almost exclusively.[29]

Negatively charged oxygen on phosphorus is much more effective than alkyl groups. Metallated phosphine oxides such as 285 are considerably more nucleophilic than the normal alkylidene triphenylphosphoranes, since replacement of a phenyl group by the electron-releasing oxygen results in a strongly increased contribution of the limiting structure 285b to the resonance hybrid.[223–225,332,333]

$$\underset{285a}{(C_6H_5)_2\overset{\overset{O^{\ominus}}{\|}}{P}=CHC_6H_5} \longleftrightarrow \underset{285b}{(C_6H_5)_2\overset{\overset{O}{\|}}{P}-\overset{\ominus}{C}HC_6H_5}$$
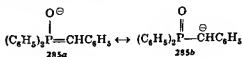
Reaction of benzophenone with 285, for instance, gives triphenylethylene in 70% yield.[224] The other product, diphenylphosphinate ion,

[332] Horner, Hoffmann, and Wippel, Ger. pat. 1,079,030 (to Farbw. Hoechst), 1958.
[333] Horner, Hoffmann, and Klink, Ger. pat. 1,138,757 (to Farbw. Hoechst) [C.A., 58, 9143 (1963)].

is water-soluble. Unlike the normal diphenylalkylphosphine oxides,

$$(C_6H_5)_2\overset{\overset{\displaystyle O^{\ominus}}{|}}{P}=CHC_6H_5 + (C_6H_5)_2C=O \rightarrow (C_6H_5)_2C=CHC_6H_5 + (C_6H_5)_2\overset{\overset{\displaystyle O^{\ominus}}{|}}{P}=O$$

285a
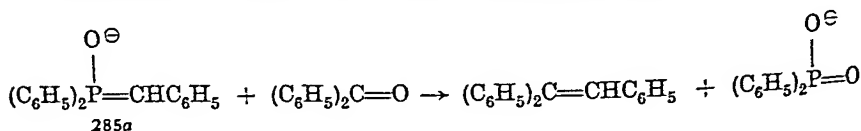
which are readily obtained by the alkaline decomposition of the corresponding triphenylalkylphosphonium salts, phosphine oxides containing groups capable of resonance cannot be prepared by this route. Since these phosphine oxides are not easily obtainable, their reactions have so far attained only theoretical importance. Although normal diphenylalkylphosphine oxides can be metallated and used for the preparation of olefins, they are inferior to the ylides.

Alkylphosphonic acid esters, which can be obtained from triethyl phosphite by an Arbuzow reaction, can in certain cases be metallated and made to react with carbonyl compounds to give olefins in a reaction similar to that of phosphine oxides.[223-226,332-334] Thus ethyl bromoacetate reacts with triethyl phosphite to give diethyl carbethoxymethyl phosphonate (286) in good yield. The phosphonate 286 can be converted to the anion 287 with sodium hydride in glycol dimethyl ether. Unlike the corresponding phosphorane, which will react with ketones only under forcing conditions, the anion 287 is strongly nucleophilic and reacts with cyclohexanone at room temperature within a few minutes to give ethyl cyclohexylidene acetate (132) in 70% yield.[226] The diethyl phosphate

$$(C_2H_5O)_3P + BrCH_2CO_2C_2H_5 \longrightarrow C_2H_5Br + (C_2H_5O)_2\overset{\overset{\displaystyle |}{|}}{\underset{\underset{\displaystyle O}{||}}{P}}-CH_2CO_2C_2H_5$$

286

$$(C_2H_5O)_2\overset{\overset{\displaystyle |}{|}}{\underset{\underset{\displaystyle \ominus O}{|}}{P}}=CHCO_2C_2H_5 \longleftrightarrow (C_2H_5O)_2\overset{\overset{\displaystyle |}{|}}{\underset{\underset{\displaystyle O}{||}}{P}}-\overset{\ominus}{C}HCO_2C_2H_5$$

287a   287b

$$\bigcirc=CHCO_2C_2H_5 + (C_2H_5O)_2\overset{\overset{\displaystyle |}{|}}{\underset{\underset{\displaystyle O^{\ominus}}{|}}{P}}=O$$

132   288
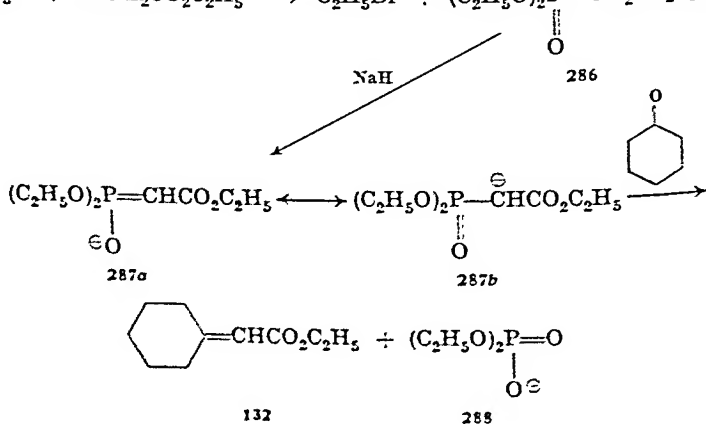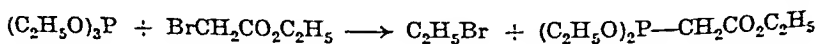
The first instance of an asymmetric induction in a Wittig reaction was observed when the reaction was used with the optically active ethyl (p-menth-3-yloxycarbonylmethyl)phosphonate (289).[335] The levorotatory isomer of the substituted cyclohexylideneacetic acid 290 was formed predominantly.
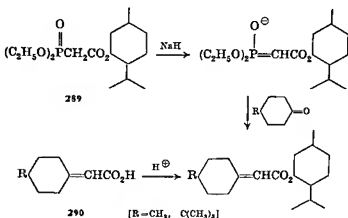
Sodium amide[223,336] and potassium t-butoxide[224,225,332,333] have also been used in place of sodium hydride. Potassium t-butoxide has the disadvantage that it leads to resinification with aliphatic ketones such as acetone and cyclohexanone.[225]

The metallated diethyl carbethoxymethylphosphonate (287) proved to be superior to carbethoxymethylenetriphenylphosphorane in its reactivity toward other ketones also[37,103] and has been used for the synthesis of a series of α,β-unsaturated esters.[225,336,337] α,β-Unsaturated nitriles can be obtained in an analogous manner;[336,338,339] such nitriles are accessible from cyanomethylenetriphenylphosphorane only if aldehydes are used as the carbonyl component. In general, the phosphonate ester reaction will be the method of choice for the interaction of resonance-stabilized reagents with ketones. In all other cases the normal alkylidene triphenylphosphoranes are to be preferred, in accord with the theory of the mechanism of the Wittig reaction. Alkylphosphonic acid esters, for instance, are completely unsuitable for the preparation of olefins.[225]

The phosphonate ester method has found application, particularly in industry,[252,263] in the synthesis of α,β-unsaturated carboxylic esters,

[335] Tömösközi and Janzso, Chem. Ind. (London), 1962, 2085.
[336] Takahashi, Fujisawa, and Ohta, Bull. Chem. Soc. Japan, 35, 1498 (1962).
[337] Stilz and Pommer, Ger. pat. 1,109,671 (to BASF) [C.A., 56, 8571a (1962)].
[338] Stilz and Pommer, Ger. pat. 1,108,208 (to BASF) [C.A., 56, 11422e (1962)].
[339] Pommer and Stilz, Ger. pat. 1,116,652 (to BASF) [C.A., 57, 2267d (1962)].

nitriles, and stilbenes.[340] Distyrylbenzenes[333,341–345] and polyenes[346] have also been prepared from the corresponding bifunctional phosphonate esters.

In an analogous manner phenyldiethoxyphosphine (291) can be converted to phosphinic acid ethyl esters such as ethyl cyanomethylphenylphosphinate (292), which is related to both the phosphine oxides and the phosphinate esters and thus undergoes the same reactions. For instance, it reacts with β-ionone to give β-ionylideneacetonitrile (293) in 87% yield.[347] The phosphinic acid esters have therefore been used for

the same olefin-forming reactions as the phosphonate esters.[225,348–352]

The central atom of the Wittig reagents itself has also been varied. The stability of fluorenylidenetriphenylarsorane (294), which can be obtained by the action of aqueous sodium hydroxide on the arsonium salt, is similar to that of the corresponding phosphorane; decomposition into triphenylarsine oxide and fluorene occurs only on prolonged heating with aqueous alcoholic sodium hydroxide. Its reactivity toward carbonyl compounds is about the same as that of fluorenylidenetri-n-butylphosphorane, since it reacts even with such a poor electrophile as p-dimethylaminobenzaldehyde to give p-dimethylaminobenzalfluorene (295) in 97% yield.[353]

[340] Seus and Wilson, J. Org. Chem., 26, 5243 (1961).
[341] Stilz and Pommer, Ger. pat. 1,108,219 (to BASF) [C.A., 57, 732c (1962)].
[342] Pommer, Stilz, and Stolp, Ger. pat. 1,108,220 (to BASF) [C.A., 56, 14165d (1962)].
[343] Stilz, Pommer, and König, Ger. pat. 1,112,072 (to BASF) [C.A., 56, 2378d (1962)].
[344] Stilz and Pommer, Ger. pat. 1,124,949 (to BASF) [C.A. 57, 3358c (1962)].
[345] Stilz, Stolp, and Pommer, Ger. pat. 1,129,947 (to BASF) [C.A., 57, 16502f (1962)].
[346] Stilz and Pommer, Ger. pat. 1,092,472 (to BASF) [C.A., 56, 413b (1962)].
[347] Pommer and Stilz, Ger. pat. 1,116,653 (to BASF) [C.A., 57, 2267d (1962)].
[348] Stilz and Pommer, Ger. pat. 1,116,654 (to BASF) [C.A., 57, 737a (1962)].
[349] Stilz and Pommer, Ger. pat. 1,117,122 (to BASF) [C.A., 57, 2143c (1962)].
[350] Pommer and Stilz, Ger. pat. 1,117,580 (to BASF) [C.A., 57, 4591d (1962)].
[351] Stilz and Pommer, Ger. pat. 1,122,065 (to BASF) [C.A., 57, 3358a (1962)].
[352] Pommer and Stilz, Ger. pat. 1,122,524 (to BASF) [C.A., 57, 3484h (1962)].
[353] Johnson, J. Org. Chem., 25, 183 (1960).

$$\underset{\textbf{294}}{\text{(fluorenylidene=As(C}_6\text{H}_5)_3)} + p\text{-}(CH_3)_2NC_6H_4CHO \longrightarrow$$

$$\underset{\textbf{295}}{\text{(fluorenylidene=CHC}_6\text{H}_4\text{N(CH}_3)_2\text{-}p)} + (C_6H_5)_3AsO$$

The betaine **296** obtained from methylenetriphenylarsorane and benzophenone can decompose by two different paths.[354] After acid hydrolysis,

$$(C_6H_5)_3As\!=\!CH_2 + (C_6H_5)_2C\!=\!O \longrightarrow \underset{\textbf{296}}{\overset{(C_6H_5)_3\overset{\oplus}{As}\!-\!CH_2}{\underset{\ominus O-C(C_6H_5)_2}{|}}}$$

$$(C_6H_5)_3AsO + (C_6H_5)_2C\!=\!CH_2 \qquad (C_6H_5)_3As + \underset{}{(C_6H_5)_2C\!-\!CH_2}$$

$$\overset{H^{\ominus}}{\downarrow}$$

$$(C_6H_5)_2CHCHO$$

the products from path A and path B are obtained in about a 1:3 ratio. With antimony as the central atom, the reaction proceeds almost exclusively by path B and 1,1-diphenylethylene and triphenylstibine oxide are formed only in traces.[354]

Such an abnormal decomposition of a betaine will occur even in a resonance-stabilized ylide if sulfur is used as the central atom.[355,356] In
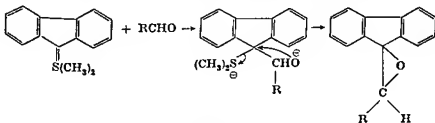
[354] Henry and Wittig, *J. Am. Chem. Soc.*, **82**, 563 (1960).
[355] Johnson and LaCount, *Chem. Ind. (London)*, **1958**, 1440.
[356] Johnson and LaCount, *J. Am. Chem. Soc.*, **83**, 417 (1961).

addition, a Sommelet rearrangement has been observed.[356] Epoxides have been obtained also from other sulfur ylides and carbonyl compounds.[357–359] Dimethylsulfoxonium methylide (297), which has recently been prepared from trimethylsulfoxonium halides, has proved to be particularly useful; epoxides were obtained in 70–90% yields from carbonyl compounds.[360]

$$(CH_3)_3\overset{\oplus}{\underset{X^\ominus}{S}}{=}O \xrightarrow{\text{NaH}} (CH_3)_2\overset{O}{\overset{\|}{S}}{=}CH_2 \xrightarrow{\underset{R_2}{\overset{R_1}{>}}C=O}$$

$$\underset{R_2}{\overset{R_1}{>}}\underset{\underset{O}{\diagdown\diagup}}{C{-}CH_2} + (CH_3)_2SO$$

297

With benzalacetophenone the cyclopropane derivative 298 was obtained in 95% yield.[360]

$$(CH_3)_2\overset{O}{\overset{\|}{S}}{=}CH_2 + C_6H_5CH{=}CHCOC_6H_5 \rightarrow \underset{CH_2}{\overset{C_6H_5CH{-}CHCOC_6H_5}{\diagdown\diagup}}$$

297   298

The methylene group in methylene triphenylphosphoranes has also been replaced by isoelectronic groups. Triphenylphosphine imine (299), for instance, reacts with benzophenone to give benzophenone imine (300).[361] Reaction with an α-keto ester gives an α-imino ester which, on catalytic hydrogenation, is converted to an α-amino ester as illustrated by the synthesis of the alanine ester 301.[362]

$$(C_6H_5)_3\overset{\ominus}{\underset{Cl^\ominus}{P}}NH_2 \xrightarrow{\text{NaNH}_2} (C_6H_5)_3P{=}NH \xrightarrow{(C_6H_5)_2CO} (C_6H_5)_2C{=}NH$$

299   300

$$\downarrow \text{CH}_3\text{COCO}_2\text{CH}_3$$

$$\underset{NH}{\overset{\|}{CH_3CCO_2CH_3}} \xrightarrow{\text{H}_2} \underset{NH_2}{\overset{|}{CH_3CHCO_2CH_3}}$$

301

Substituted triphenylphosphine imines such as N-phenyltriphenyl-phosphineimine (302) have previously been made to react with a number

).

of carbonyl compounds,[8,363,364] as illustrated by the conversion of diphenylketene to N-phenyldiphenylketene imine (303).

$$(C_6H_5)_3P=NC_6H_5 + (C_6H_5)_2C=C=O \rightarrow (C_6H_5)_2C=C=NC_6H_5$$

<div style="text-align:center">302   303</div>
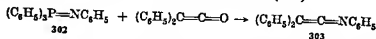
Diethyl phosphoric acid amide anions (304)[365] and even N-sulfinyl derivatives (305)[366] undergo the corresponding reaction. In the latter case sulfur dioxide is formed as a by-product.

$$(C_2H_5O)_3\overset{\overset{O^{\ominus}}{|}}{P}=NR \qquad R-N=S=O$$

<div style="text-align:center">304   305</div>

Wittig reagents have also been made to react with a number of compounds that undergo reactions similar to those of carbonyl compounds. For example, thiobenzophenone reacts with methylenetriphenylphosphorane to give 1,1-diphenylethylene.[13,138]

$$(C_6H_5)_3P=CH_2 + (C_6H_5)_2C=S \rightarrow (C_6H_5)_2C=CH_2 + (C_6H_5)_3PS$$

<div style="text-align:center">(76%)   (82%)</div>
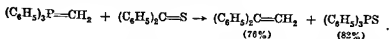
Carbon disulfide is converted to thioketenes; thus fluorenylidenetriphenylphosphorane gives the dimeric thioketene 306 in 68% yield.[367]
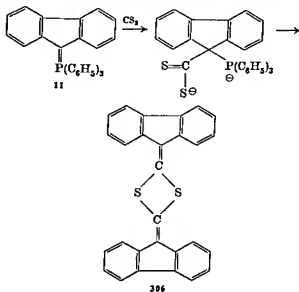
[363] Staudinger and Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).
[364] Staudinger and Meyer, *Ber.*, **53**, 72 (1920).
[365] Wadsworth, Jr., and Emmons, *J. Am. Chem. Soc.*, **84**, 1316 (1962).
[366] Kresze and Albrecht, *Angew. Chem.*, **74**, 781 (1962).
[367] Schönberg, Frese, and Brosowski, *Chem. Ber.*, **95**, 3077 (1962).

With isocyanates, the expected ketene imines are obtained only in a few cases.[7,8]

$$(C_6H_5)_3P{=}C(C_6H_5)_2 \ + \ C_6H_5N{=}C{=}O \ \rightarrow \ C_6H_5N{=}C{=}C(C_6H_5)_2$$

Methylenetriphenylphosphorane or alkylidene phosphoranes, which contain a hydrogen atom on the methylene group, undergo a Michael addition to the C=N linkage of phenyl isocyanate.[41]

$$(C_6H_5)_3P{=}CH_2 \ + \ 2C_6H_5N{=}C{=}O \ \longrightarrow \ \underset{\underset{P(C_6H_5)_3}{\overset{\|}{}}}{C_6H_5NHC\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}NHC_6H_5}$$

$$(C_6H_5)_3P{=}CHCO_2C_2H_5 \ + \ C_6H_5N{=}C{=}O \ \xrightarrow{90\%} \ \underset{\underset{O=CNHC_6H_5}{|}}{(C_6H_5)_3P{=}CCO_2C_2H_5}$$

Nitrosobenzene reacts with alkylidene triphenylphosphoranes to give Schiff bases (azomethines) which can be hydrolyzed to give aldehydes or ketones.[13,185,363] For instance, benzylidenetriphenylphosphorane is converted to benzaldehyde by way of benzalaniline. This is a general

$$(C_6H_5)_3P{=}CHC_6H_5 \ + \ C_6H_5N{=}O \ \rightarrow \ C_6H_5N{=}CHC_6H_5 \ \xrightarrow{H^{\ominus}}$$
$$C_6H_5CHO \ + \ C_6H_5NH_3^{\ominus}$$

method for the preparation of carbonyl compounds. Geranylidenetriphenylphosphorane, for example, has been converted to citral.

Resonance-stabilized alkylidene phosphoranes react analogously with nitrosobenzene, as illustrated by the conversion of diphenylmethylene-triphenylphosphorane to benzophenone anil (307).[369]

$$(C_6H_5)_3P{=}C(C_6H_5)_2 \ + \ C_6H_5N{=}O \ \rightarrow \ \underset{307}{C_6H_5N{=}C(C_6H_5)_2}$$

Nitromethylene triphenylphosphoranes give rise to products containing a carbon-nitrogen triple bond in a reaction which is similar to the formation of acetylenes by an intramolecular Wittig reaction of acyl-methylene triphenylphosphoranes. For example, nitrobenzylidenetriphenylphosphorane (308), in the presence of triphenylphosphine, gives benzonitrile in 75% yield.[45]

$$(C_6H_5)_3P=CC_6H_5 \leftrightarrow (C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}-C_6H_5$$

308a   **308b**

$$\downarrow$$

$$C_6H_5C\equiv\overset{\oplus}{N}=\overset{\ominus}{O} \xrightarrow{(C_6H_5)_3P} C_6H_5CN$$

Finally, mention should be made of the reaction of alkylidene phosphoranes with epoxides for which an intermediate betaine similar to that occurring in the Wittig reaction has been proposed.[370,371] Styrene oxide and other epoxides react with carbethoxymethylenetriphenylphosphorane to give cyclopropanecarboxylic esters.

$$(C_6H_5)_3P=CHCO_2C_2H_5 + RCH\overset{O}{\diagup}\diagdown CH_2 \rightarrow \overset{(C_6H_5)_3\overset{\oplus}{P}-CHCO_2C_2H_5}{\underset{\ominus O-CHR}{\overset{|}{CH_2}}} \rightarrow$$

$$\overset{(C_6H_5)_3P-CHCO_2C_2H_5}{\underset{R}{\overset{|}{CH_2}}} \rightarrow RCH-CHCO_2C_2H_5$$
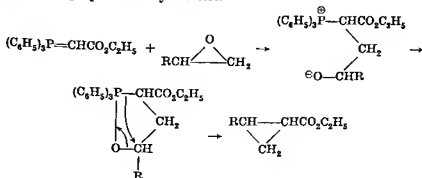
Ethyl norcaranecarboxylate (**309**) is formed in 56% yield from cyclohexene oxide.[371] Metallated phosphonate esters[226] and phosphine

$$\overset{O}{\diagup}\diagdown + (C_6H_5)_3P=CHCO_2C_2H_5 \rightarrow \text{(bicyclic structure) } CHCO_2C_2H_5$$
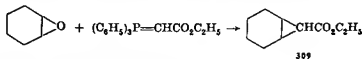
oxides[372] undergo analogous reactions.

Methylethylphenylbenzylidenephosphorane (**310**), on the other hand, reacts with styrene oxide to give mainly benzylacetophenone (**311**) and only a small amount of 1,2-diphenylcyclopropane. A possible mechanism is shown on p. 388.[373,374]

[370] Denney and Boskin, *J. Am. Chem. Soc.*, **81**, 6330 (1959).
[371] Denney, Vill, and Boskin, *J. Am. Chem. Soc.*, **84**, 3944 (1962).
[372] Horner, Hoffmann, and Toscano, *Chem. Ber.*, **95**, 536 (1962).
[373] McEwen and Wolf, *J. Am. Chem. Soc.*, **84**, 676 (1962).
[374] McEwen, Bladé-Font, and Vander Werf, *J. Am. Chem. Soc.*, **84**, 677 (1962).
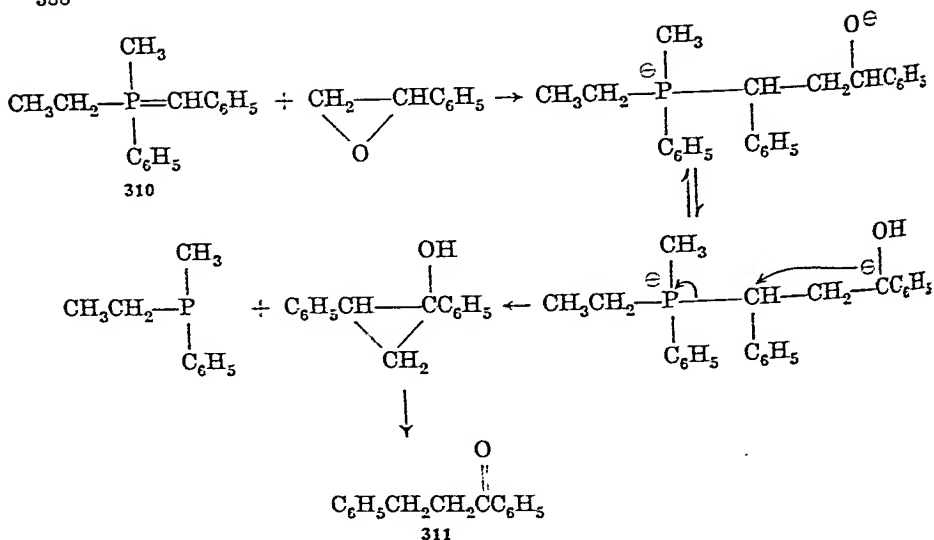
EXPERIMENTAL CONDITIONS

Preparation of Phosphonium Salts

Triphenylalkylphosphonium salts are generally prepared from triphenylphosphine and alkyl halides.

$$(C_6H_5)_3P + RX \rightarrow (C_6H_5)_3\overset{\oplus}{P}R \quad X^{\ominus}$$
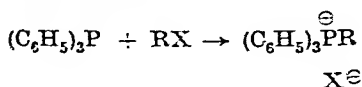
The rate of reaction decreases in the series $RI > RBr > RCl$. The alkyl bromides are used most frequently because they are often more readily accessible than the alkyl iodides. In general, three methods may be used for this reaction.

1. Liquid halides may be made to react with triphenylphosphine without the use of a solvent.

2. The reaction of solid halides with triphenylphosphine may be carried out in the melt.

3. Equimolar quantities of triphenylphosphine and an alkyl halide are allowed to react in a suitable solvent.

The first two modes of preparation are customarily used only if the third method fails to give the desired phosphonium salts. For example, 1,4-dibromobutane and triphenylphosphine react in benzene to give the monophosphonium salt 312 in quantitative yield,[74] whereas heating the reactants without a solvent gives rise to the bis-phosphonium salt 313 in

90% yield.[52] The bis-phosphonium salt 313 can also be prepared from

$$Br(CH_2)_4Br + (C_6H_5)_3P \xrightarrow{\text{Benzene}} (C_6H_5)_3\overset{\oplus}{P}(CH_2)_4Br$$
$$Br^{\ominus}$$
312

No solvent ↓

$$(C_6H_5)_3\overset{\oplus}{P}-(CH_2)_4-\overset{\oplus}{P}(C_6H_5)_3$$
$$Br^{\ominus} \qquad\qquad Br^{\ominus}$$
313
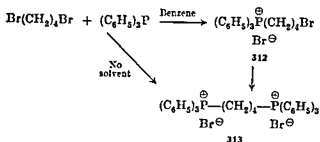
the monophosphonium salt 312 and triphenylphosphine either in the melt[74] or in a different solvent.[301] In solvents of low polarity, such as benzene, xylene, or diethyl ether, bis-halides generally form the pure monophosphonium salts if they are insoluble in the solvent.[375] Strongly polar solvents, such as nitrobenzene, acetonitrile, or dimethylformamide, however, keep the mono salt in solution so that reaction with a second equivalent of triphenylphosphine can take place. For example, reaction of 1,4-dibromobutane with 2 moles of triphenylphosphine in acetonitrile furnishes the bis-phosphonium salt 313 directly in quantitative yield.[225] Suitable choice of solvents will thus make it generally unnecessary to carry out the reaction in the melt. In chloroform, mixtures of mono- and di-phosphonium salts are often formed.

In addition to its polarity, the boiling point of a solvent is also of great importance since it determines the maximum reaction temperature unless the reaction is carried out under pressure. The interaction of ω,ω'-dibromoxylenes with triphenylphosphine proceeds much less readily in ether than in xylene. Some alkyl halides, however, give good yields only if ether is the solvent.[241] In such reactions it is advantageous to carry out the reaction in a sealed tube at 100–120°.[71 72 241]

Nitromethane,[41,48,155,192] formic acid,[225] acetic acid,[376] ethyl acetate,[236,377] ethanol,[54,79] acetone,[29] butanone or cyclohexanone,[301] benzonitrile,[159] toluene,[378] and tetrahydrofuran[69,209,287] have been used as solvents. The salts precipitate either spontaneously or on addition of diethyl ether.

Alkyl bromides may undergo an allylic rearrangement during the quaternization, as illustrated by the reaction of 1-bromo-2-methylene-cyclohexane.[70,153]

[375] Friedrich and Henning, *Chem. Ber.*, 92, 2756 (1959).

[376] Brit. pat. 812,268 (to Hoffmann-La Roche) [*C.A.*, 53, 18983f (1959)].

[377] Isler, Chopard-dit-Jean, Montavon, Ruegg, and Zeller, *Helv. Chim. Acta*, 40, 1256 (1957).

[378] Bergmann and Dusza, *J. Org. Chem.*, 23, 1245 (1958)

$$\text{(structure: methylenecyclohexane with Br)} + (C_6H_5)_3P \rightarrow \text{(cyclohexene with } CH_2\overset{\oplus}{P}(C_6H_5)_3 \text{) } Br^{\ominus}$$
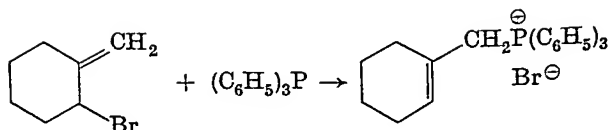
Complications may also occur in the interaction of triphenylphosphine with α-halocarbonyl compounds. Whereas primary α-bromo- and α-chloro-ketones give the desired products,[31] reaction of secondary and tertiary α-halocarbonyl compounds with triphenylphosphine in the presence of water or alcohol leads to the dehalogenated carbonyl compounds.[379-381]

$$(C_6H_5)_3P + BrCH_2COC_6H_5 \longrightarrow (C_6H_5)_3\overset{\oplus}{P}CH_2COC_6H_5$$
$$Br^{\ominus}$$

$$(C_6H_5)_3P + ClCH_2COCH_3 \longrightarrow (C_6H_5)_3\overset{\oplus}{P}CH_2COCH_3$$
$$Cl^{\ominus}$$

$$\text{(2-bromocyclohexanone)} + (C_6H_5)_3P \xrightarrow{ROH} \text{(cyclohexanone)} + (C_6H_5)_3PO + RBr$$

$$C_6H_5CCl_2COC_6H_5 + (C_6H_5)_3P \xrightarrow{H_2O}$$
$$C_6H_5CHClCOC_6H_5 + (C_6H_5)_3PO + HCl$$
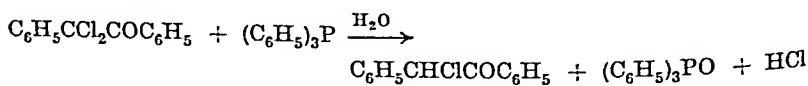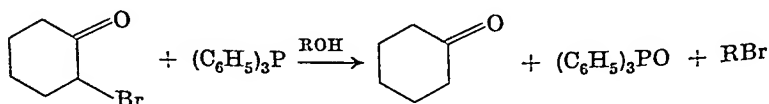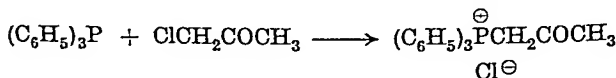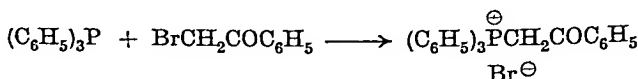
Formation of a triple bond may occur in the absence of water or alcohol.[382] Not only α-halo ketones but also 1-bromo-1-nitroalkanes and N-bromoamides react with triphenylphosphine in this way.[382]

$$C_6H_5CHClCOC_6H_5 + (C_6H_5)_3P \xrightarrow{90\%}$$
$$C_6H_5C\equiv CC_6H_5 + (C_6H_5)_3PO + HCl$$

$$C_6H_5CHBrNO_2 + 2(C_6H_5)_3P \xrightarrow{75\%}$$
$$C_6H_5C\equiv N + (C_6H_5)_3PO + (C_6H_5)_3PO\cdot HBr$$

$$C_6H_5CONHBr + (C_6H_5)_3P \longrightarrow C_6H_5C\equiv N + (C_6H_5)_3PO\cdot HBr$$
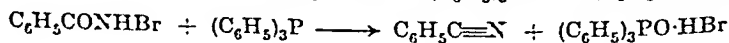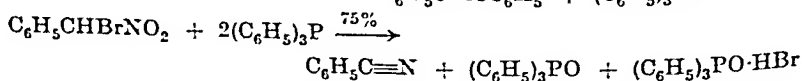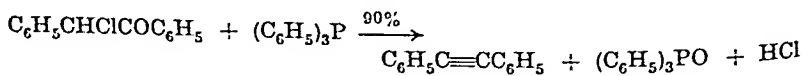
Trichloroacetamides react with phosphines and phosphites to give trichlorovinylamines.[283]

$$Cl_3CCONR_2 + R_3'P \rightarrow Cl_2C=C\overset{\displaystyle Cl}{\underset{\displaystyle NR_2}{}} + R_3'PO$$
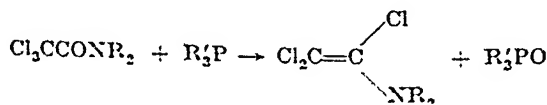
The mechanism of these reactions may involve initial removal of a halogen cation by triphenylphosphine;[384] for instance,

$$Cl_3CCONR_2 + R_3'P \rightarrow R_3'\overset{\oplus}{P}Cl + Cl_2C=\overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\underset{\displaystyle NR_2}{|}}{C}} \rightarrow$$

$$\rightarrow Cl_2C=\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle NR_2}{|}}{C}} + R_3'PO$$
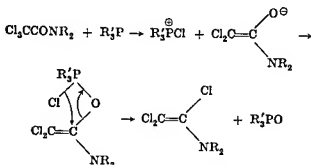
Such a course appears to be followed in the reaction of phenacyl bromide with triphenylphosphine in methanol, whereas phenacyl chloride in methanol undergoes simple displacement of chloride to form the phosphonium salt.[385]

$$(C_6H_5)_3\overset{\oplus}{P}CH_2COC_6H_5$$
$$Cl^{\ominus}$$
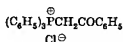
Halomethylphosphonium salts prepared from dihalomethanes and triphenylphosphine are often contaminated by the bis-phosphonium salt.[61]

$$3(C_6H_5)_3P + 2CH_2Br_2 \rightarrow \underset{\underset{(40\%)}{Br^{\ominus}}}{(C_6H_5)_3\overset{\oplus}{P}CH_2Br} + \underset{\underset{(20\%)}{Br^{\ominus}\quad Br^{\ominus}}}{(C_6H_5)_3\overset{\oplus}{P}—CH_2—\overset{\oplus}{P}(C_6H_5)_3}$$
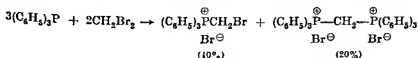
The pure compounds can be prepared from the corresponding hydroxymethylphosphonium salts with thionyl chloride or a phosphorus pentahalide.[64,92]

$$\underset{Cl^{\ominus}}{(C_6H_5)_3\overset{\oplus}{P}CH_2OH} \xrightarrow[63\%]{SOCl_2} \underset{Cl^{\ominus}}{(C_6H_5)_3\overset{\oplus}{P}CH_2Cl}$$

$$\underset{Br^{\ominus}}{(C_6H_5)_3\overset{\oplus}{P}CH_2OH} \xrightarrow[74\%]{PBr_3} \underset{Br^{\ominus}}{(C_6H_5)_3\overset{\oplus}{P}CH_2Br}$$
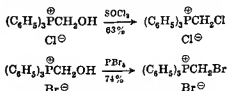
Mention is made of an elegant method for the preparation of phosphonium salts from alcohols, which are made to react either with

[384] Speziale and Smith, J. Am. Chem. Soc., 84, 1868 (1962)
[385] Borowitz and Virkhaus, J. Am. Chem. Soc., 85, 2184 (1963).

triphenylphosphine hydrohalides or with triphenylphosphine in the presence of proton donors such as hydrogen halides or sulfuric acid.[386]

$$ROH + (C_6H_5)_3\overset{\oplus}{P}H$$
$$X^{\ominus} \searrow$$
$$(C_6H_5)_3\overset{\oplus}{P}R + H_2O$$
$$X^{\ominus}$$
$$ROH + (C_6H_5)_3P + HX \nearrow$$
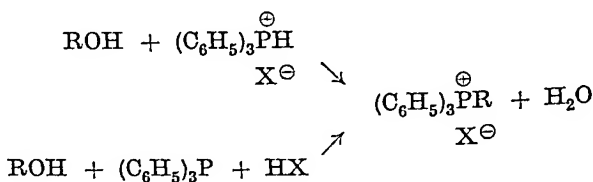
The water is removed either by azeotropic distillation or with silica gel or acetic anhydride. Thus β-ionol and triphenylphosphine hydrochloride react in acetonitrile to give β-ionyltriphenylphosphonium chloride (314).[291]

314
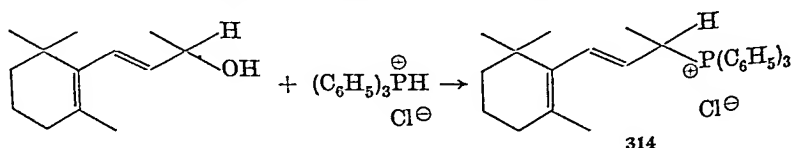
Axerophthyltriphenylphosphonium chloride (315) is obtained in quantitative yield by the reaction of vitamin A with triphenylphosphine and hydrogen chloride in ethanol.[128,266]

315
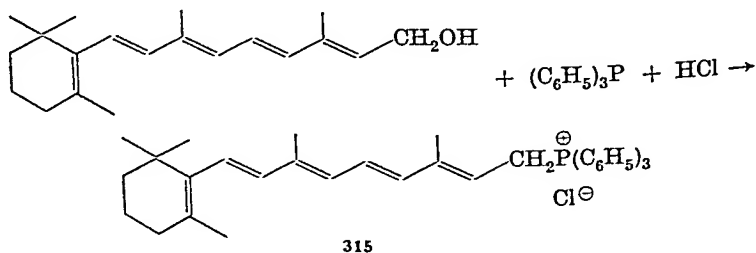
Starting from vinyl-β-ionol (316), (β-ionylideneëthyl)triphenylphosphonium halides (317) are obtained by an allylic rearrangement.[264,263,285,286,294,397]

316

317
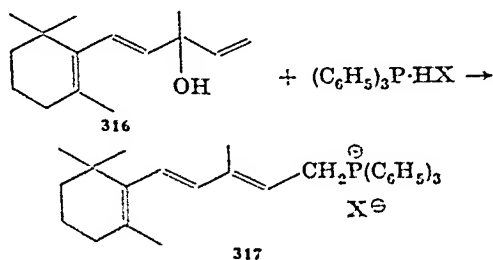
The addition of triphenylphosphine hydrohalides to conjugated systems also leads to phosphonium salts.[240,266,269,284,292]
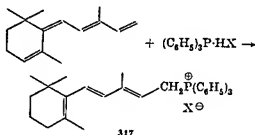
Addition may also occur to a monoölefin provided that it is sufficiently activated.[333]

$$(C_6H_5)_3P + CH_2=CHR \rightleftharpoons (C_6H_5)_3\overset{\oplus}{P}CH_2\overset{\ominus}{C}HR \xrightarrow{HX} (C_6H_5)_3\overset{\oplus}{P}-CH_2CH_2R$$
$$X^{\ominus}$$

$$(R = CO_2H, CO_2CH_3, CONH_2, CN, NO_2)$$
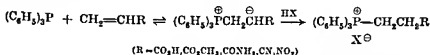
Similarly, the reaction of triphenylphosphine with paraformaldehyde in the presence of hydrogen chloride gives rise to hydroxymethyltriphenylphosphonium chloride (318).[92]

$$(C_6H_5)_3P + CH_2O + HCl \rightarrow (C_6H_5)_3\overset{\oplus}{P}CH_2OH$$
$$Cl^{\ominus}$$
$$318$$
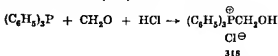
Thorough washing with benzene usually suffices to purify the phosphonium salts. Purer products are obtained by recrystallization from higher alcohols or tetrahydrofuran or by precipitating the salts from their solutions in chloroform, methanol, or other suitable solvents by addition of ether, acetone, or ethyl acetate. Some phosphonium salts are hygroscopic, or they crystallize with the inclusion of solvent molecules and must be dried well under vacuum before they can be used.

The Wittig Reaction

As a rule, the Wittig reagents are not isolated; immediately following their generation, they are allowed to react with carbonyl compounds in the same reaction vessel.

The Organometallic Method. In this method, phenyllithium or *n*-butyllithium is the usual proton acceptor, and diethyl ether or tetrahydrofuran the solvent. For smaller runs, Schlenk tubes (Fig. 1) have proved to be useful; they are sealed and, if necessary, heated in a water

[333] Hoffmann, *Chem. Ber.*, 94, 1331 (1961).

bath. Larger runs are made in a three-necked flask fitted with stirrer, reflux condenser, addition funnel, and nitrogen inlet tube. If higher reaction temperatures are necessary, the ether must be replaced by a higher-boiling solvent.

The carefully dried and pulverized phosphonium salt is suspended in, for instance, diethyl ether or tetrahydrofuran and an equivalent of a diethyl ether solution of n-butyillthium or, preferably, phenyllithium is added under nitrogen. Ylide formation, which usually occurs instantaneously, is evidenced by disappearance of the phosphonium salt with the formation of a red or orange solution.

The ylide solution or suspension so obtained is then treated with the carbonyl compound. As a rule, the phosphonium betaine precipitates immediately. Decomposition of the betaine often occurs in the cold, especially if the newly formed double bond is resonance-stabilized. Heating to 60–70° may be necessary.

When diethyl ether is the solvent, the triphenylphosphine oxide precipitates as a crystalline adduct with 1 mole of lithium halide and may be removed by filtration. The filtrate contains the olefin.

Other solvents which keep triphenylphosphine oxide in solution are best removed by distillation after the reaction is complete. The residue is then extracted with petroleum ether in which triphenylphosphine oxide and lithium halides are insoluble.

N_2

FIG. 1

The Alkoxide Method. This method uses the alkali metal alkoxides as proton acceptors and the corresponding alcohols as solvents. Either the phosphonium salt and the carbonyl compound are dissolved in alcohol and then treated with one equivalent of an alcoholic solution of the alkali metal alkoxide, or the components are added successively or simultaneously to the alkoxide solution.

With sparingly soluble carbonyl compounds, it is best to dilute the alcohol with a suitable solvent such as methylene chloride or dimethylformamide. Since base is used in the reaction, its consumption may be followed acidimetrically. Aldehydes and ketones that resinify in the presence of alkoxides should not be subjected to the alkoxide procedure but can readily be used in a modified organometallic method.[259]

The isolation procedure depends on the properties of the resulting olefin. If the olefin is insoluble, it can be isolated by filtration. Triphenylphosphine oxide remains in solution on the addition of up to 40% water and can thus be separated from olefins that are insoluble in
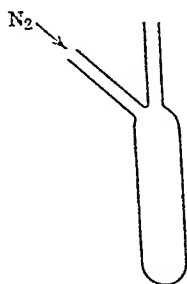
aqueous alcohol. The solvent may be removed by vacuum distillation and the olefin isolated from the residue by distillation, crystallization, chromatography, or extraction with low-boiling petroleum ether.

Reactions with Resonance-Stabilized Phosphoranes. Acylmethylene and carbalkoxymethylene triphenylphosphoranes are stable toward water and precipitate as crystalline solids on addition of a base to an aqueous solution of the corresponding phosphonium salt. They may be recrystallized from a mixture of ethyl acetate and petroleum ether. Their reaction with carbonyl compounds may be carried out by heating in a suitable solvent such as benzene or tetrahydrofuran. It is not necessary to isolate the phosphorane; the reaction may be carried out just as well by any of the previously described methods.

EXPERIMENTAL PROCEDURES

Methylenecyclohexane.[2] *Method A* (*Using n-Butyllithium*). This preparation is described in *Organic Syntheses*, **40**, 66 (1960).

Method B (*Using Sodium Hydride in Dimethyl Sulfoxide*)[63] Sodium hydride (0.10 mole as a 55% dispersion in mineral oil) in a 300-ml. three-necked flask is washed with several portions of n-pentane to remove the mineral oil. The flask is then equipped with rubber stoppers, a reflux condenser fitted with a three-way stopcock, and a magnetic stirrer. The system is alternately evacuated and filled with nitrogen; 50 ml. of dimethyl sulfoxide is introduced via syringe, and the mixture is heated at 75–80° for ca. 45 minutes, or until the evolution of hydrogen ceases. The resulting solution of methylsulfinyl carbanion is cooled in an ice-water bath, and 35.7 g. (0.10 mole) of methyltriphenylphosphonium bromide in 100 ml. of warm dimethyl sulfoxide is added The resulting dark red solution of the ylide is stirred at room temperature for 10 minutes before use.

Freshly distilled cyclohexanone, 10.8 g (0.11 mole), is added to 0.10 mole of methylenetriphenylphosphorane, and the reaction mixture is stirred at room temperature for 30 minutes and immediately distilled under reduced pressure to give 8.10 g. (86.3%) of methylenecyclohexane, b.p. 42°/105 mm., which is collected in a solid carbon dioxide trap

2,2'-Distyrylbiphenyl.[191] To a suspension of methylenetriphenylphosphorane, prepared from 0.1 mole of triphenylmethylphosphonium bromide and 0.12 mole of phenyllithium in 200 ml of diethyl ether, is added, under nitrogen, 13.5 g (37.3 mmoles) of 2,2'-dibenzoylbiphenyl, and the mixture is shaken at room temperature for 3 days. The adduct of triphenylphosphine oxide and lithium bromide is removed by centrifugation and the ethereal solution washed with water The ether is

removed and the residue crystallized twice from ethanol to give 11.4 g. (85.5%) of 2,2'-distyrylbiphenyl, m.p. 100–101°.

o-Divinylbenzene.[52] Triphenylmethylphosphonium bromide (55 mmoles) is added to a solution of 2.34 g. (60 mmoles) of sodium amide in 300 ml. of liquid ammonia. The ammonia is removed, the residue is dissolved in 200 ml. of absolute diethyl ether and heated under reflux for 30 minutes. To the orange-yellow solution of methylenetriphenylphosphorane is added with stirring over a period of 15 minutes a solution of 3.75 g. (28 mmoles) of o-phthalaldehyde in 100 ml. of absolute diethyl ether. The mixture is then heated under reflux for 2 hours. The filtered solution is concentrated to 50 ml. and again filtered. From the filtrate, 2.7 g. (75%) of o-divinylbenzene, b.p. 75–78°/14 mm., n_D^{20} 1.5765, is obtained by distillation.

4,4'-Divinylbiphenyl.[187]   A.   *Biphenyl-4,4'-bis-(methyltriphenylphosphonium chloride)*. A mixture of 6.3 g. of 4,4'-bis(chloromethyl)biphenyl, 14.2 g. of triphenylphosphine, and 50 ml. of dimethylformamide is heated with stirring under reflux for 3 hours. The phosphonium salt begins to precipitate after about 20 minutes. After the reaction mixture has cooled, the salt is collected by filtration, washed with absolute benzene, and dried under vacuum at 80°. The yield is 85%.

B. *4,4'-Divinylbiphenyl*. To a solution of 4 g. of the phosphonium salt in 120 ml. of absolute ethanol are added successively 20 ml. of a 15% solution of formaldehyde in ethanol and 40 ml. of 0.3M ethanolic lithium ethoxide. After about 10 minutes the yellow-orange mixture deposits 4,4'-divinylbiphenyl in the form of colorless, shining leaflets. The mixture is diluted with 50 ml. of water and allowed to stand in a refrigerator overnight. The precipitate is collected by filtration and washed with 50% ethanol, giving 4,4'-divinylbiphenyl, m.p. 153°, in 80% yield.

Benzylidenecyclopentane.[155] Triphenylcyclopentylphosphonium iodide (18.3 g., 40 mmoles) in 60 ml. of absolute ether is treated under nitrogen with 40 mmoles of n-butyllithium. Solution of the salt and formation of the dark red cyclopentylidenetriphenylphosphorane occur within 2 hours. A solution of 4.3 g. (40.5 mmoles) of benzaldehyde in 10 ml. of absolute ether is added dropwise with cooling, and the mixture is then allowed to stand at about 30° for 10 hours. The clear solution is decanted from the triphenylphosphine oxide, shaken three times with 20-ml. portions of 40% aqueous sodium bisulfite solution, and then washed with water until neutral. Removal of the ether from the dried (calcium chloride) solution followed by vacuum distillation gives 4.1 g. (65%) of benzylidenecyclopentane, b.p. 123–124°/17 mm., n_D^{21} 1.5770.

Lycopene.[275] To a suspension of 100 g. of geranyltriphenylphosphonium bromide in 1 l. of absolute ether is added with stirring 200 ml. of a $1N$ ethereal phenyllithium solution. After it has been stirred for 1 hour, the dark red solution of geranylidenetriphenylphosphorane is treated within 5 minutes with a solution of 20 g. of crocetin dialdehyde in 500 ml. of anhydrous methylene chloride. The mixture is then stirred for 15 minutes at 30° and heated under reflux for 5 hours. Methanol (600 ml.) is added in one portion to the warm solution, which is then cooled to 10° with stirring. The crystalline mass is collected by filtration under carbon dioxide. The crude lycopene is dissolved in 300 ml. of acid-free methylene chloride at a temperature not higher than 40° and then reprecipitated with 500 ml. of methanol. The yield of lycopene, m.p. 172–173°, is 25 g.

***trans*-4-Nitro-4′-methoxystilbene.**[166] Butyllithium (0.85 g., 0.013 mole) is added under nitrogen to a suspension of 4.3 g. (0.01 mole) of *p*-nitrobenzyltriphenylphosphonium chloride in benzene and the mixture stirred for 2 hours. Anisaldehyde (1.63 g., 0.012 mole) is added, and the mixture is stirred at room temperature for 4 hours and then diluted with petroleum ether. The dark precipitate is collected and crystallized from ethanol, giving 2.23 g. (89%) of *trans*-4-nitro-4′-methoxystilbene in the form of yellow crystals, m.p. 131–132.5°

1,4-Diphenyl-1,3-butadiene.[66] To a solution of sodium ethoxide prepared from 1.5 g. (65.3 mmoles) of sodium and 100 ml. of absolute ethanol is added 18.8 g. (48.3 mmoles) of triphenylbenzylphosphonium chloride. The yellow mixture is stirred vigorously for 5 minutes, and an ethanolic solution of 6.6 g. (50 mmoles) of cinnamaldehyde is added dropwise, resulting in a disappearance of the color. In the course of 30 minutes more at room temperature the mixture assumes a tan coloration. The amount of 1,4-diphenylbutadiene, m.p 150°, isolated is 8 4 g. (84%).

1,2-Distyrylbenzene.[201a] *A. o-Xylylene-bis-(triphenylphosphonium bromide).* A solution of 66.1 g. (0.25 mole) of o-xylylene dibromide and 142.5 g. (0.55 mole) of triphenylphosphine in 500 ml of dimethylformamide is heated under reflux for 3 hours. The colorless salt, which starts precipitating within 10–15 minutes, is collected by filtration after cooling and washed successively with dimethylformamide and ether The yield of phosphonium salt, m.p. >340°, is 175.9 g (89%).

B. 1,2-Distyrylbenzene. To a solution of 42 5 g. (0 054 mole) of the bis-phosphonium salt and 12.6 g. (0.119 mole) of benzaldehyde in 150 ml. of absolute ethanol is added 500 ml of an ethanolic 0 4M solution of lithium ethoxide. The mixture is allowed to stand at room temperature for 30 minutes and is then heated under reflux for 2 hours The orange-red solution is concentrated under vacuum to 100 ml, and 300 ml. of water

is added; the yellow oil that separates is extracted with ether. The ether is removed, and the residual oil is chromatographed on aluminum oxide. Elution with low-boiling petroleum ether and recrystallization from aqueous ethanol give 12.7 g. (84%) of 1,2-distyrylbenzene in the form of colorless needles, m.p. 117–119°.

p-bis-(4-Carbomethoxystyryl)benzene.[193]   To a solution of 54 g. (0.121 mole) of 4-carbomethoxybenzyltriphenylphosphonium chloride and 6 g. (0.0448 mole) of terephthalaldehyde in 600 ml. of ethanol is added 600 ml. of 0.2M ethanolic lithium ethoxide. A pale yellow crystalline precipitate forms immediately. Water (600 ml.) is added after 30 minutes, the precipitate is collected by filtration and washed with 200 ml. of 60% ethanol. The yield of *p*-bis-(4-carbomethoxystyryl)benzene, m.p. 290°, is 13 g. (73%).

p-bis-(4-Phenylbutadienyl)benzene.   *Method A.   From p-*$C_6H_4[CH{=}P(C_6H_5)_3]_2$.[210]   A solution of lithium ethoxide prepared from 1.74 g. (0.25 mole) of lithium wire, and 1 *l*. of ethanol is added to a solution of 70 g. (0.10 mole) of *p*-xylylene-bis(triphenylphosphonium chloride) and 35 g. (0.26 mole) of cinnamaldehyde in 250 ml. of ethanol. After the reaction mixture has been left at room temperature for 12 hours, the yellow precipitate is collected by filtration, washed with 300 ml. of 60% ethanol, and dried under vacuum at 70°. The yield is 29–32 g. (87–95%). The crude product may be converted to the all-*trans* isomer with iodine in xylene; after crystallization from dimethylformamide, it melts at 290–293°.

Method B.   From Terephthalaldehyde.[66]   To a solution of sodium ethoxide prepared from 1 g. (43.5 mmoles) of sodium and 120 ml. of absolute ethanol are added successively 19 g. (41.4 mmoles) of triphenyl-cinnamylphosphonium bromide and a solution of 3 g. (22.4 mmoles) of terephthalaldehyde in 40 ml. of absolute ethanol. The mixture is heated to 80° for 20 minutes, and the solids are collected by filtration and washed with water and a little ethanol. On crystallization from xylene, 6.0 g. (87%) of *p*-bis-(4-phenylbutadienyl)benzene, m.p. 278–279°, is obtained in the form of yellow needles.

1-Chloro-2,6-dimethyl-1,5-heptadiene.[390]   To a mixture of 346 g. of triphenylchloromethylphosphonium chloride, 86 g. of piperidine (previously dried over sodium), and 400 ml. of diethyl ether a solution of 1 mole of phenyllithium in 900 ml. of diethyl ether is added dropwise at room temperature over a period of 3 hours. After 1 hour, a solution of 126 g. of 2-methylhept-2-en-6-one in 100 ml. of diethyl ether is added over a period of 2½ hours and the mixture is stirred overnight. The crystalline precipitate is collected by filtration and washed with ether. The ether

¹⁹³ G. Köbrich and W. E. Breckoff, unpublished research.

and piperidine are removed from the filtrate by distillation, low-boiling petroleum ether is added to the residue, and the triphenylphosphine oxide, which precipitates after a few hours in a refrigerator, is removed. Chromatography on aluminum oxide followed by distillation gives 134 g. (85%) of 1-chloro-2,6-dimethyl-1,5-heptadiene as a colorless liquid, b.p. 69–72°/14 mm., n_D^{20} 1.4687.

Methoxymethylenecyclohexane.[246,248] To a suspension of 21.25 g. (62 mmoles) of methoxymethyltriphenylphosphonium chloride in 200 ml. of absolute ether is added under nitrogen at room temperature a solution of 60 mmoles of phenyllithium in ether. The reaction is slightly exothermic, and part of the orange-yellow methoxymethylenetriphenylphosphorane precipitates from the dark red solution. After 10 minutes the mixture is cooled to −30°, and 5.88 g. (60 mmoles) of cyclohexanone in 10 ml. of ether is added dropwise. The triphenylphosphine oxide is removed by filtration after 15 hours at room temperature. Distillation of the filtrate gives 5.4 g. (71%) of methoxymethylenecyclohexane, b.p. 74°/48 mm., n_D^{20} 1.4707.

A small sample is heated in ether with 70% perchloric acid, and the hexahydrobenzaldehyde so obtained is converted to its 2,4-dinitrophenylhydrazone, m.p. 168–169°, in 84% yield

2-Benzyl-5-phenyl-2,4-pentadienoic Acid.[40] *A. Benzylcarbomethoxymethylenetriphenylphosphorane* Benzyl bromide (1.5 ml.) is added to a solution of 5 g. of carbomethoxymethylenetriphenylphosphorane in ethyl acetate, and the mixture is heated under reflux for 5 hours. The precipitate of triphenylcarbomethoxymethylphosphonium bromide (2.69 g., 87%) is removed by filtration, the filtrate is concentrated under vacuum, and the residue is digested several times with ethyl acetate. The yield of ylide, m.p. 186–187°, is 2.8 g (75%).

B. 2-Benzyl-5-phenyl-2,4-pentadienoic Acid A mixture of 10 g. of the ylide, 3.23 ml of cinnamaldehyde, and 400 ml. of ethyl acetate is heated under reflux under nitrogen for 24 hours The solvent is removed from the extracts, and the residue is heated under reflux with 10% aqueous methanolic potassium hydroxide for 1 hour. After cooling, a ten-fold amount of water is added, and the remaining triphenylphosphine oxide that precipitates is removed by filtration The filtrate is concentrated to 100 ml., cooled, acidified with sulfuric acid, and extracted with ether. The dienoic acid (5.2 g., 83.3%) is isolated from the dried ether extracts in the form of cream-colored needles, m.p. 180–181°

Phenylpropiolic Acid. *Method A. Via α-Bromocinnamic Acid.*[117] (a) *Bromocarbomethoxymethylenetriphenylphosphorane.* To a vigorously stirred solution of 3.35 g. (10 mmoles) of carbomethoxymethylenetriphenylphosphorane in 50 ml. of benzene is added 0.8 g. (5 mmoles) of

bromine. The precipitated phosphonium salt is removed by filtration, and the filtrate is concentrated to dryness. The oily residue solidifies after a short period to give 1.6 g. (77%) of the crystalline bromo ylide.

(b) *Phenylpropiolic Acid.* A mixture of 4.15 g. of the bromo ylide, 1.1 g. of benzaldehyde, and 30 ml. of benzene is heated under reflux for 2 hours. The solvent is removed by distillation, and the residue is heated under reflux with 4 g. of potassium hydroxide in 30 ml. of methanol for 4 hours. The methanol is removed under vacuum, and the residue is extracted with 50 ml. of water. Acidification of the aqueous solution gives a precipitate of 1.2 g. (82% yield) of phenylpropiolic acid in the form of fine colorless needles, m.p. 136–138°.

Method B. By Intramolecular Wittig Reaction.[330,331] (a) Benzoyl-carbomethoxymethylenetriphenylphosphorane. Carbomethoxymethyl-enetriphenylphosphorane (6.7 g., 20 mmoles) is dissolved in 50 ml. of dry benzene with warming. To the cooled solution is added dropwise with vigorous stirring a solution of 10 mmoles of benzoyl chloride in 10 ml. of benzene. The mixture is left at room temperature for 3 hours, and the precipitated phosphonium salt is removed by filtration. The ylide, m.p. 136–137°, is isolated from the filtrate in 74% yield.

(b) *Phenylpropiolic Acid.* The ylide (1.0 g.) is heated to 220–260° at 0.05 mm. pressure for 15 minutes. The distillate is dissolved in methanol, 3 ml. of concentrated sodium hydroxide solution is added, and the mixture is allowed to stand at room temperature for 24 hours. The methanol is removed under vacuum, and 30 ml. of water is added. The triphenylphosphine oxide is removed by filtration, and the filtrate is acidified with a small amount of concentrated hydrochloric acid, giving phenylpropiolic acid, m.p. 135–136°, in 73% yield.

Ethyl Cyclohexylideneacetate.[226] To a suspension of 2.4 g. (0.05 mole) of sodium hydride in 100 ml. of dry glycol dimethyl ether is added dropwise at room temperature 11.2 g. (0.05 mole) of diethyl carbethoxy-methylphosphonate. The mixture is stirred for 1 hour until gas evolution stops, and then 4.9 g. (0.05 mole) of cyclohexanone is added dropwise at a rate to keep the temperature below 30°. The mixture is stirred at room temperature for 15 minutes, during which time a viscous oil separates. A large excess of water is added, the ether layer is separated, dried with magnesium sulfate, and distilled under vacuum to give 5.8 g. (70%) of ethyl cyclohexylideneacetate, b.p. 88–90°/10 mm., n_D^{25} 1.4704.

TABULAR SURVEY

Tables I and II list mainly those phosphonium salts, $[(C_6H_5)_3PR]X$, that have been used as starting materials for the Wittig reaction. The

entries are arranged in the order of increasing number of carbon atoms in the alkyl group R. Within each group of salts having the same number of carbon atoms in the alkyl group, the entries follow the Beilstein system.

Tables III, IV, and V also list alkylidene phosphoranes that have not been used in Wittig reactions with carbonyl compounds.

Table VI deals only with those ylides that have been used to prepare olefins. The entries are arranged in the order of increasing number of carbon atoms in the alkylidene portion of the ylide. Under each ylide the olefins prepared from it are listed in the order of increasing number of carbon atoms in the olefin. In this table are also included olefins for whose preparation no details were given in the original reports.

In all the tables, yields are entered only when they were reported in percentages in the original reference.

The literature has been reviewed to January 1, 1963, and some later work has been included. Work reported in patents has been included only when the patent description was detailed. Because of the nature of the topic being reviewed, it is difficult to avoid missing occasional isolated examples of the Wittig reaction. It is hoped that these omissions are few.
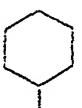
TABLE I

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES

A. Monophosphonium Salts

Carbon Atoms in R	R	X	Solvent, Time, Temperature, °C.	Yield, %	References
C$_1$	CH$_3$	Br	None, 2 days, 20	75	2
			C$_6$H$_6$, 4 days, 20	89	308, 309
	CHCl$_2$	Br	None, 4 hr, reflux	—	94
	CH$_2$Br	Br	None, 18 hr, 60	40	81
	CHBr$_2$	Br	None, reflux	85	391
	CH$_2$NO$_2$	Br	C$_6$H$_6$, 0	—	41
C$_2$	C$_2$H$_5$	Br	None, 15 hr, 120	96	178
			C$_6$H$_6$, 20 hr, 135	89	164
			C$_6$H$_5$CH$_3$, 1 day, 105	90	378
			C$_6$H$_6$, 2 days, 20	—	307
	CH$_2$CH$_2$Br	Br	Xylene, reflux	49	375
	CH$_2$CH$_2$OH	Cl	None, 2 hr, reflux	80	392, 393
	CH$_2$OCH$_3$	Cl	C$_6$H$_6$, 60 hr, 50	86	92, 247
	CH$_2$SCH$_3$	Cl	C$_6$H$_6$, 30 hr, 80	77	92
	CH$_2$CHO	Cl	CHCl$_3$, 5 hr, reflux; 12 hr., 20	—	33, 58
	CH$_2$CONH$_2$	Cl	C$_6$H$_6$, 8 hr, reflux	—	243
			CH$_3$NO$_2$, 30 hr, reflux	—	41
	CH$_2$CN	Cl	C$_6$H$_6$, 8 hr, reflux	Quant.	42, 243
			CH$_3$NO$_2$, 5 hr, reflux	—	41
		Br	C$_6$H$_6$, 2 weeks, 20	95	43
C$_3$	CH(CH$_3$)$_2$	Br	None, 24 hr, 150	—	305
		I	None, 20 hr, 100	94	178
	CH$_2$CH$_2$CH$_2$Br	Br	C$_6$H$_6$, reflux	63	375

C₄				
CH₂CH=CH₂	Br	C₂H₆, 12 hr., 20; 1 hr., reflux	92	2
CH₂C(OC)CH₃	Br	C₂H₆, 8 hr., reflux	80	393
CH₂COCH₃	Cl	CHCl₃, 45 min., reflux	—	31
CH₂CO₂CH₃	Br	C₂H₆, 12 hr., 20	—	30
C₃H₇ⁿ	Br	CH₃NO₂, 10 hr., reflux	70	182
(CH₃)₂Cl	Cl	C₂H₆, reflux	61	130, 375
(CH₃)₃Br	Br	C₂H₆, reflux	—	375
CH₂C=CHCH₃	Br	C₂H₆, 14 hr., 20	0	375
	Br	C₂H₆, 48 hr., 20	Quant.	74
CH₂C(CH₃)=CH₂	Cl	C₂H₆, 14 hr., reflux	84	181
CH₂CH=ClCH₂Br	Cl	C₂H₆, 7 days, reflux	89	328
CH₂CH₂OCOCH₃	Br	C₂H₆, 14 hr., reflux	—	304
CH₂CO₂C₂H₅	Br	Nonε, 4 hr., reflux	84–88	230
	Br	C₂H₆, 5 hr., reflux	—	392
	Br	C₂H₆, 7 days, 20	—	243
	Cl·2H₂O	C₂H₆, 30 min., reflux	89	395
	Br	C₂H₆, 12 hr.	—	3
CH((CH₃)₂CO₂CH₃	Br	Nonε, 5 min., 89	—	39, 50, 60
		C₃H₆, 2 hr., 70	—	302
C₅				
CH₂CH(CH₃)₂	Br	Xylene, 15 hr., 100	58	321
	I	C₆H₅CH₃, 1 day, 115	—	378
CH₂CH=CH(CH₃)₂	Br	(C₂H₅)₂O, 2 days, 20	—	260
CH(OC₂H₅)₂	Br	C₂H₆, 30 hr., 20	—	265
(CH₃)₃AOH	I	C₂H₆, 15 hr., reflux	70	248
CH₂AOHC₂H₅	Br	C₂H₆, 3 hr., reflux	—	138
CH(CH₃)ACO₂H₅	Br	Nonε, 5 min., 100	—	392
CH₂CH=CHCO₂CH₃	Br	C₂H₆, 2 hr., 70	—	30
	Br	C₂H₆, 1 day, 20	90	232, 234, 235

Note: References 391 to 404 are on p. 400.

TABLE I—Continued

Phosphonium Salts from Triphenylphosphine and Alkyl Halides

A. Monophosphonium Salts—Continued
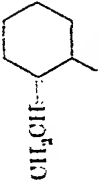
Carbon Atoms in R	R and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C_3 (contd.)	(cyclopentyl)	I	None, 6 hr., 115	40	185
	$CH_3CH=CHC_3H_7\text{-}n$ (cyclopentyl)	Br	CH_2Cl_2, 6 hr., reflux	—	46, 47
C_9	$C_9H_{15}\text{-}n$	Br	—	—	327
	$CH_3CH=CHC_3H_7\text{-}n$	Br	C_6H_6, 20–30 hr., 20	96	161, 325
			C_6H_6, 30 min., reflux	94	326
	$CH_3CH_2CH=C(CH_3)_2$	I	C_6H_6, 3 hr., reflux	88	192
	$(CH_3)_3C(CH_3)_2)=CH_2$	I	C_6H_6, 3 hr., reflux	89	192
	$CH_3C=CC_3H_7\text{-}n$	Br	C_6H_6, few days, 20	95	325
	$CH_2(CH=CH)_2CH_3$	Br	C_6H_6, 2 days, 20	90	181
	$CH_2CH=C(CH_3)C=CH$	Br	C_6H_6, 30 min., reflux	Quant.	328
			$CH_3CO_2C_2H_5$, 1 day, 20	—	377
			CH_3CO_2H	—	378
	$CH_2C(CH_3)=CHCH_2OCH_3$	Br	$(C_2H_5)_2O$, 12 hr., 20	—	286a
	$CH_2C(CH_3)=CHCO_2CH_3$	Br	C_6H_6, 1 day, 20	—	282
	$CH_3CH=C(CH_3)CO_2CH_3$	Br	C_6H_6, 1 day, 20	77–82	232, 235
	$CH(CH_3)CH=CHCO_2CH_3$	Br	C_6H_6, 2–3 days, 20	71–77	233, 234
	(cyclohexyl)	I	None, 5 hr., 140; 30 hr., 170	72	185
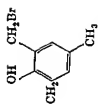
		Conditions	Yield (%)	References
C₇				
$(CH_3)_2CH=CH_2$	Br	$(C_2H_5)_2O$, 2 days, 100	—	100
$CH_3CH=CHC_4H_9\text{-}n$	Br	C_2H_6	70	258
$CH_3CH=C(CF_3)CH(OC_2H_5)C_2H_5)_{1/2}$	Br	$(C_2H_5)_2O$, 10 hr, 20; 4 hr, reflux	70	216
$CH_3CH=CHC(\ )=CHCH_3$	Br	THF, 12 hr, 20	—	287
$CH_3C\equiv CC(CH_3)=CHCH_3$	Br	C_2H_6, 2 hr, 40	60	209
(cyclohexene)	Br	C_2H_6, 1 day, 20	59	158, 314
$C_6H_5CH_3$	Cl	None	Quant.	375
$CH_3C_6H_4Cl\text{-}2,4$	Cl	DMF, 12 hr; 1 hr, 100	68	201
$C_5H_4NO_2\text{-}p$	Cl	$CHCl_3$, 12 hr, 20	70	220
	Cl	C_2H_6, reflux	58	375
	Br	C_2H_6, 2 hr, reflux	80	166
$C_6H_5CH_2NO_2\text{-}p$	Cl	$CHCl_3$, few min, 100	95	220
		Xylene, 20 hr, reflux	80	210
		$(C_2H_5)_2O$	—	243
$CH_3OC_6H_4CH_3$	Br	$(C_2H_5)_2O$, 30 hr, 100	71	71
C₈				
$CH_2CH(CH_2Cl)_2$	Br	$CH_3CO\cdot C_2H_5$, 1 day, 20	—	236
$CH_2CH=C(CH_3)CH_2CH=CHCO_2CH_3$	Br	C_2H_6, 12 hr, 20	—	183, 184
(cyclohexane =CH₂)		C_2H_6, 2 days, 20	—	158
HO (cyclohexanol =CH₂)	Br	THF, 12 hr, 20	—	69

Note: References 391 to 404 are on p. 400.
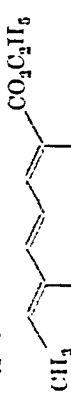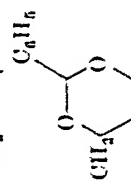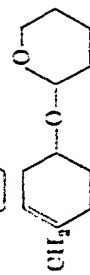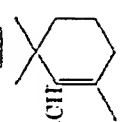
TABLE I—Continued

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES

A. Monophosphonium Salts—Continued

Carbon Atoms in R	R and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C_8 (contd.)	$CH_3C_6H_3(CH_3-m)$	Br	None	Quant.	375
	$CH_3C_6H_3(CH_3-p)$	Cl	Xylene, 12 hr, reflux	85–90	105
	$CH_2C_6H_4CH_2Br-o$	Br	DMF, 3 hr, reflux	70	210
	$CH_2C_6H_4CH_2Br-m$	Br	C_6H_6, 8 hr, reflux	92	201a
	$CH_2C_6H_4CH_2Br-p$	Br	Xylene, reflux	38	375
	$CH_2C_6H_4OCH_3-p$	Br	Xylene, reflux	94	375
	$CH_2OC_6H_4CH_3-p$	Cl	C_6H_6, 4 hr, reflux	92	166
		Cl	$(C_2H_5)_2O$	96	248
	$CH_2C_6H_3O_2CH_2-3,4$	Br	DMF, 30 min., 60	—	201
	$CH_2C_6H_4CHO-p$	Cl	CH_3NO_2, 2 days, 80	84	396
	$CH_2COC_6H_5$	Br	$CHCl_3$	—	31
	$CH_2CH=CHC_2H_5-n$	Br	C_6H_6	44	257
	$CH_2CH=CH(CH_2)_4CH=CH_2$	Br	$(C_2H_5)_2O$, several days, 20	60	100
C_9	cyclohexane ring with $CH_2CH=$ and CH_2OH	Br	$THF/(C_2H_5)_2O$, 12 hr, 20	—	69
	$CH_2CH=CHC_6H_5$	Cl	Xylene, 12 hr, reflux	91–93	210
		Br	C_6H_6, 2 hr, reflux	82	138
			None	Quant.	375

		C6H6, reflux	97	375

Compound / Group	Halide	Conditions	Yield (%)	Refs.
(benzene ring: OH, CH2Br, CH3)	Br			
CH2C6H3(OCH3)2,2,4	Br	DMF, 1 hr, 20; 30 min., 60	—	201
CH2C6H3(OCH3)(CHO)2,4	Cl	Xylene, 20 hr, reflux	—	208
CHC6H3(COCH3	Br	C6H6, 12 hr, reflux	97	330
CH2C6H4COC6H5	Br	C6H6, 3 hr, reflux	69	203
CH2C6H4CO2C6H5-p	Cl	Xylene, 1 day, reflux	92	103
C10				
CH2CH=C(CH3)CH2CH2CH11[1]	Br	DMF or (CH3)2SO, 3 hr., 80	—	199, 200
CH2CH=CH(CH3)CH2CH2CH2CH=C(CH3)2	Br	C6H6, 2 days, 20	—	276
	Br	C6H6, 2 days, 20	—	275, 276
(cyclohexene with CH3 groups)		C6H6, 6-8 hr., 20	96	397
CH2CH2CH(C≡C)C6H5-n	Br	C6H6, 30 min., reflux	77	328
CH2CH=CH(C=O)C6H5CH=CHCH3	Br	(C2H5)2O, 12 hr., 120	—	241
	Br	C6H6, 12 hr., 20	—	259
	Br	C6H6, 2 days, 20	—	275
C11				
CH2(CH=CH)2C6H5-β	Br	C6H6, 1 hr., 60	Quant.	209
CH2CH=CH(C=O)C6H5[2]	Br	C6H6, 30 min., reflux	70	328
CH2C6H4-β	Br	(C2H5)2O, 12 hr., 20	—	181
	Br	(C2H5)2O, 1 day, 20	—	180
CH2C6H4-β	Br	Xylene, reflux	93	197
(CH2)3COC6H5	Br	None, 88 hr., 100	71	202

Note: References 391 to 404 are on p. 490.

TABLE I—*Continued*

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES

A. Monophosphonium Salts—Continued

Carbon Atoms in R	R and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C_{12}	$C_{12}H_{25}$-*n*	Br	C_6H_5CN, 3 hr, 140–150	—	150
		Br	$CH_3CO_2C_2H_5$, 1 day, 20	—	236
		I	$(C_2H_5)_2O$, 3 days, 100	88	72
		Br	C_6H_6, 2 days, 20	—	70
C_{13}	$CH(CH_3)CH=CH$	Br	THF, 2 hr, reflux $(C_2H_5)_2O$, 5 hr, 20; 30 min., 80–90	— —	200 280
	$CH(C_6H_5)_2$	Br	None, 100	50	88
	$CH(C_6H_5)C_6H_4NO_2$-*p*	Br	Xylene, 5 hr, reflux	—	44

	Halide	Conditions	Yield	References
(fluorene with CH₃) CH(OC₂H₅)₂ CH=C(C₂H₅)₂	Br	C₆H₆, 1 hr, reflux	50	88
		CH₃NO₂, 2 hr, 20	—	48
	Cl	C₆H₆, 8 hr, 20	82	87
	Br	(C₂H₅)₂O*	7	123
C₁₄ CH₃CH=C(CH₃)CH₂CH₂CH₃	Br	C₆H₆, 12 hr, reflux	—	205
C₁₅ CH₃CH=C(CH₃)CH₂CH₂CH=CH	Cl	DMF, 12 hr, 20	—	283
	Br	DMF, C₆H₆, or (C₂H₅)₂O, 1 day, 20	—	54, 283, 287
CH₃C₆H₄(CH=CHC₆H₅)-m	Br	C₂H₅OH, 1 day, 20	46	54
CH₃C₆H₄(CH=CHC₆H₅)-p	Cl	C₆H₆, reflux		375
CH₃CH=C(C₆H₅)₂	Br	Xylene, 10 hr, reflux	80	195
	Br	Xylene, 3–4 hr, reflux	87–90	196
	Br	Xylene, 4 hr, reflux	93–95	211

Note. References 391 to 401 are on p. 490.

* The halide (C₆H₅)₂C=CHBr in ether was converted to the Grignard reagent, THF was added, and the solution was added to triphenylphosphine in ether. Oxygen was bubbled through the reaction mixture which was then decomposed with hydrobromic acid.

TABLE I—*Continued*

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES

A. Monophosphonium Salts—Continued

Carbon Atoms in R	R and R in [(C₆H₅)₃PR]X	X	Solvent, Time, Temperature, °C.	Yield, %	References
C₁₆	$CH_2C_6H_4$	(CH=CHC₆H₄CH₃-*p*)	Br	Xylene, 3–4 hr, reflux	83–85	196
C₁₇	CH₂C₆H₄(CH=CH CHC₆H₅)-*m*	Br	C₆H₆, reflux	10	375
	CH_2		Br	Xylene, 2 hr, reflux	80	197
C₁₈	CH₂CO₂C₁₀H₂₃-*n*	Br	C₆H₆, 12 hr, 20	—	30
C₁₉	CH(CH₃)CO₂C₁₆H₃₃-*n*	Br	C₆H₆, 2 hr, 70	—	30
C₂₀	CH₂CH₃	Br	C₆H₆, 4 days, 20	—	267
C₂₃	CH_2 [—CH CH]₂ H	Br	Xylene, 2 hr, reflux	75–80	198

B. Bis-phosphonium Salts

Carbon Atoms in R	—R—	X in $[(C_6H_5)_3P{-}R{-}P(C_6H_5)_3]X_2$	Solvent, Time, Temperature, °C.	Yield, %	References
C$_1$	CH_2	Br	None, 150	40	81
C$_2$	CH_2CH_2	Br	None, 30 min, 140	82	52
			C$_6$H$_6$, 4 days, reflux	—	210
C$_3$	CH_2OCH_2	Br	—	—	190
	$CH_2CH_2CH_2$	Br	None, 30 min, 180	77	52
			DMF, 5 days, 80–90		375
		Cl	DMF, 3 hr, reflux	94	225
C$_4$	CH_2COCH_2	Cl	CHCl$_3$, 2 hr, reflux	8	79
	$CH_2CH_2CH_2CH_2$	Cl	None, 25 hr, 160	51	185
		Br	None, 30 min, 250	90	52, 74, 302
			Cyclohexanone, 48 hr, reflux	77	300, 301
			CH$_3$CN, 36 hr, 90	65	225
			Xylene, 60 hr, reflux	94	210
			THF, 16 hr, reflux	41	209
		Br	None, 1 hr, 250	Quant.	230
	$CH_2CH{=}CHCH_2$		DMF		212
C$_5$	$CH_2(CH_2)_3CH_2$	Br	CH$_3$CN, 60 hr, 90	54	225
C$_6$	$CH_2(CH_2)_4CH_2$	Br	HCO$_2$H, 12 hr, 110	74	225
	$CH_2CO_2CH_2CH_2OCOCH_2$	Cl	C$_6$H$_5$OH, 1 day, reflux	98	79
C$_8$	CH_2—C$_6$H$_4$—CH_2	Br	DMF, 3 hr, reflux	89	201a

TABLE I—Continued

B. *Bis-phosphonium Salts—Continued*

Carbon Atoms in R	—R— in $[(C_6H_5)_3P—R—P(C_6H_5)_3]X_2$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C_8 (*contd.*)		Cl	DMF, 3 hr, reflux	93–98	193
		Br	DMF, 30 min, 150.	89	375
		Br	$C_6H_5NO_2$, 30 min, 150	84	375
C_9		Br	DMF, 3 hr, 150	95	375
		Br	$C_6H_5NO_2$, 15 min, 150	94	375
C_{10}		Br	C_6H_6, 6 hr, 40–45; 12 hr, 20	90	80, 271
		Br	C_6H_6, 6 hr, 40–45; 12 hr, 20	—	80, 271
		Cl	DMF, 2.5 hr, reflux	94	193

	Structure	Halogen	Conditions	Yield (%)	Ref.
C_{14}		Cl	DMF, 3 hr, reflux	85	187
C_{16}		Br	DMF, 3 hr, reflux	75–80	187
C_{24}		Br	DMF, 16 hr, reflux	56	201a

Note: References 391 to 404 are on p. 490.

TABLE II

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHONIUM HALIDES, $(C_6H_5)_3PHX$, AND ALCOHOLS OR POLYENES

A. Monophosphonium Salts
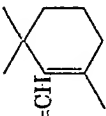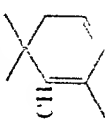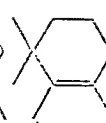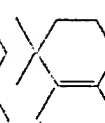
Carbon Atoms in R	R and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	References
C₇	$C_7H_9^{-n}$	Br	None	386
C₁₀	$CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$	Cl	DMF, 1 day, 20	274
		Br	THF, 14 hr., 20	368
		Br	DMF, 12 hr., 20	274
	$CH_2CH=C(CH_3)CH=CHCH=C(CH_3)_2$	Br		279
	(cyclohexene ring structure, $CH_2=$)	Br	THF, 1 day, 20	368
			DMF, 12 hr., 20	274
C₁₃	$CH(CH_3)CH=CH$ (cyclohexene ring structure)	Cl	CH₃CN, 1 hr., 20	272, 291
			DMF, 15 hr., 20*	240
			DMF, 1 hr., 0*†	240
		Br	Dimethyltetrahydrofuran, 6 hr., 20	291
			DMF, 12 hr., 20*	240, 292
			CH₃CN*	240
			$CH_3CO_2C_2H_5$, 2 days, 20*	240

C₁₃

Structure	Halide	Conditions	References
CH₃CH=C(CH₃)CH=CH (bicyclic)	Cl	THF, 6 hr, 20	285, 387
		THF, 30 hr, 5†	287
		CH₃OH, 10 hr, 20	285
		CH₃OH, 20 hr, 20†	264, 280
		C₂H₅OH, 18 hr, 20•,†	284
		C₂H₅OH, 6 hr, 20	288, 285, 294
		CH₃CN, 12 hr, 20	270
		CH₃CN, 2 days, 20•	269
		DMF, 12 hr, 20	270
		DMF, 3 hr, 20†	270
		DMF, 12 hr, 10•	284
		DMF, 3 hr, 20•,†	269
	Br	None, 15 hr, 20	285
		CTHF,60 hr., 20	387
		DMF,36 hr., 20	270
		MF, 12–24 hr., 20	268, 270, 285, 294
		DMF, 38 hr., 20•	269, 284
CH₃CH=CH₃CH=CH (bicyclic)	Br	DMF, 6 hr, 20	270
CH₃CH=C(CH₃)CH=CH (cyclohexene)	Cl	CH₃OH, 3 hr, 40; 50 hr.,†	264

Note: References 301 to 404 are on p. 490.

• The polymer corresponding to the alcohol was used.

† Instead of (C₆H₅)₃PHX, triphenylphosphine and the hydrogen halide, HX, were used.

TABLE II—Continued

PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHONIUM HALIDES, $(C_6H_5)_3PHX$, AND ALCOHOLS OR POLYENES

A. Monophosphonium Salts—Continued

Carbon Atoms in R	R and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	References
C_{15} (contd.)	$CH_2CH=C(CH_3)CH=CH$—	Br	CH_3OH, 92 hr., 20	288
	$CH_3CH=C(CH_3)CH=CH$—	Cl	CH_3OH, 60 hr., 20†	264
C_{15}	$CH(CH_3)$—	Cl	CH_3CN, 2 hr., 20	270
C_{20}	CH_2—	Cl	DMF, 8 hr., 0 DMF, 12 hr., 10* DMF, 12 hr., 5† C_2H_5OH, 1 day, 20* C_2H_5OH, 1 day, 20†	266 266 266 266 266

B. Bis-phosphonium Salt

Carbon Atoms in —R—	—R— and in $[(C_6H_5)_3P^+—R—P(C_6H_5)_3]X_2$	X	Solvent, Time, Temperature, °C.	References
C_4	$CH_2CH=CHCH_2$—	Br	C_6H_6†	386

Note: References 381 to 404 are on p. 490.

* The polyene corresponding to the alcohol was used.

† Instead of $(C_6H_5)_3PHX$, triphenylphosphine and the hydrogen halide, HX, were used.

TABLE III

Alkylidene Phosphoranes Prepared from Phosphonium Salts and Bases

A. Monophosphoranes

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C₁	(C₆H₅)₃P=CH₂	LiC₄H₉, (C₂H₅)₂O	3 hr., 20	2, 303, 304, 306
				308, 309
		LiC₄H₉-n, (C₂H₅)₂O	5 days, 20	310
			2 hr., reflux	182
			30 min., 20	41, 174
			1 hr., 20	304, 308
			2 hr., 29	130, 252,
				254, 319
		LiC₄H₉-n, THF	4 hr., 20	183, 317
		NaNH₂, liq. (C₂H₅)₂O	30 min., 20	310, 311
		NaNH₂, liq. NH₃		64
		LiC₄H₉-n, (C₂H₅)₂O		52
		Lithium piperidide, (C₆H₅)₃O		96
		LiC₄H₉, (C₂H₅)₂O		84
C₂	[C₆H₅)₃P=CHCl	LiC₄H₉-n, (C₂H₅)₂O	1 hr., 20	164
	(C₆H₅)₃P=CHCH₃	NaC(CH₃)₃, (C₂H₅)₂O	3 hr., 0	178, 307
	(C₆H₅)₃P=CHCH₃	NaOCH₃/SOCH₃, DMSO	1 hr., 20	327
				41, 306
		LiC₄H₉, THF		64
	(C₆H₅)₃P=CHOCH₃	NaOCH₃, (C₂H₅)₂O	10 min., 20	92, 240–248
		LiC₄H₉, THF		84
		LiC₄H₉-n, (C₂H₅)₂O	2 hr., −50	92
		NaOCH₃, CH₃OH		92
		LiOC₄H₉, C₆H₅OH		92
	(C₆H₅)₃P=CHSCH₃	LiC₄H₉, C₆H₅OH	15 min., 20	92, 247, 248
		LiC₄H₉, THF		92

Note: References 391 to 404 are on p. 490.

TABLE III—Continued

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES

A. *Monophosphoranes—Continued*

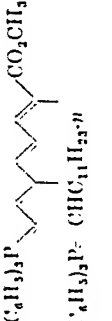| Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C_2 (contd.)	$(C_6H_5)_3P=CHCHO$	NaOH, H_2O	0	33, 58
		$(C_2H_5)_3N$, C_2H_5OH		33, 58
	$(C_6H_5)_3P=CHCONH_2$	NaOH, H_2O		41
		$NaOC_2H_5$, C_2H_5OH	10 min., 40–50	243
		NaOH, H_2O	1 hr., 20	41–43
	$(C_6H_5)_3P=CHCN$ (85)	$NaOC_2H_5$, C_2H_5OH	30 min., 20	113, 243
		$NaOC_2H_5$, C_2H_5OH		113
C_3	$(C_6H_5)_3P=CHC_2H_5$	$LiC_4H_9\text{-}n$, $(C_2H_5)_2O$	2 hr., 20	178
	$(C_6H_5)_3P=C(CH_3)_2$	LiC_4H_5, $(C_2H_5)_2O$	12 hr., 20	305
		$LiC_4H_9\text{-}n$, $(C_2H_5)_2O$	2 days, 20	150
				64
	$(C_6H_5)_3P=CHCH=CH_2$	$NaC(C_6H_5)_3$, $(C_2H_5)_2O$		2
		LiC_4H_5, $(C_2H_5)_2O$	2–3 hr., 20	259, 318
		$LiC_4H_9\text{-}n$, $(C_2H_5)_2O$	2 hr., 20	16
	$(C_6H_5)_3P=CHCH_2CH_2O^{\ominus}$	$LiC_4H_9\text{-}n$, $(C_2H_5)_2O$		281
	$(C_6H_5)_3P=CHCH_2OCH_3$	LiC_4H_5, $(C_2H_5)_2O$		33, 58
	$(C_6H_5)_3P=C(CH_3)CHO$	NaOH, H_2O		60
	$(C_6H_5)_3P=CHCOCH_3$ (70)	NaOH, H_2O	8 hr., 20	31
		Na_2CO_3, H_2O	–70	60
		Pyridine, CH_2Cl_2		39, 56, 297
	$(C_6H_5)_3P=CClCOCH_3$ (40)	NaOH, H_2O	30 min., 20	39, 231, 295, 297
	$(C_6H_5)_3P=CHCO_2CH_3$ (65)	$NaOCH_3$, CH_2Cl_2		
C_4	$(C_6H_5)_3P=CHC_3H_7\text{-}n$	LiC_4H_5, $(C_2H_5)_2O$	2 hr., reflux	182
		$LiC_4H_9\text{-}n$, $(C_2H_5)_2O$	2 hr., 20	130
		$LiC_4H_9\text{-}n$, pot. other	1 hr., 20	161, 327
	$(C_6H_5)_3P=CH(CH_2)_3Br$	LiC_4H_5, $(C_2H_5)_2O$		74
		$NaOC_2H_5$, C_2H_5OH		74
	$(C_6H_5)_3P=CHCH=CHCH_3$	$LiC_4H_9\text{-}n$, $(C_2H_5)_2$	10 min. to 3 hr., 20	71, 181, 328, 399

	Reagent	Conditions	References
C_8			
$(C_6H_5)_3P$=CHCH(CH$_3$)$_2$CH$_3$ (75)	LiC$_2$H$_5$, THF	1 hr., 20	394
$(C_6H_5)_3P$=CHCO$_2$C$_2$H$_5$ (60–70)	NaOH, H$_2$O	30 min., 20	39, 56
	NaOCH$_3$, CH$_3$Cl$_2$	10 min., 20	39, 34, 243
$(C_6H_5)_3P$=C(CH$_3$)CO$_2$CH$_3$ (44)	NaOH, H$_2$O		39, 56, 297
	KOH, H$_2$O		164
	NaOCH$_3$, CH$_3$Cl$_2$	30 min., 20	39, 231, 295–297
$(C_6H_5)_3P$=CHCO$_2$C$_2$H$_5$ (80)	$(C_2H_5)_3N$, CH$_2$Cl$_2$	–70	60
$(C_6H_5)_3P$=CHCOC$_2$H$_5$ (69)	NaOH, H$_2$O		60
$(C_6H_5)_3P$=CHCH$_2$C$_6$H$_5$-i	LiC$_2$H$_5$-n, (C$_2$H$_5$)$_2$O	30 min., 20	378
$(C_6H_5)_3P$=CHCH=CHCH$_3$	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	30 min., 20	320
$(C_6H_5)_3P$=CHCH=CHCH$_3$	NaOCH$_3$, CH$_2$Cl$_2$	3 hr., 20	321
$(C_6H_5)_3P$=CHCH=CH$_2$	LiC$_4$H$_9$-n, C$_2$H$_6$	30 min., 20	200
$(C_6H_5)_3P$=CHCH=CHC$_6$H$_5$-n	LiC$_4$H$_9$-n, C$_2$H$_6$	10 min., –10	265
	NaOCH$_3$, CH$_3$OH	10 min., –40	248
$(C_6H_5)_3P$=CHCH$_2$OCH$_3$	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O		248
$(C_6H_5)_3P$=CHCH$_2$OC$_2$H$_5$ (75–80)	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	4 hr., 20	248
$(C_6H_5)_3P$=C(CH$_3$)CO$_2$CH$_3$	NaOH, H$_2$O		248
	NaOH, CH$_2$Cl$_2$		138
	NaOCH$_3$, CH$_3$OH		39, 56
$(C_6H_5)_3P$=CHCl=CHCOC$_2$H$_5$ (70)	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	30 min., 20	232, 234, 235
		15 min., 20	242
(41)	NaOH, H$_2$O	2 hr., 20	185
C_9			
$(C_6H_5)_3P$=CHC$_5$H$_{11}$-n			46, 47
$(C_6H_5)_3P$=CHCH=CHC$_4$H$_9$-n	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	1 hr., 0	327
	NaOCH$_3$, CH$_3$OH	30 min., 0	325
	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	2–3 hr., 20	161
$(C_6H_5)_3P$=CHCH=CH=C(CH$_3$)$_2$	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	1–3 hr., 20	326
$(C_6H_5)_3P$=CHCH=(CH$_3$)CH=CH$_2$	LiC$_6$H$_5$, (C$_2$H$_5$)$_2$O	2 hr., reflux	326
	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	2 hr., reflux	182
			182

Note: References 391 to 404 are on p. 490.

TABLE III—*Continued*

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES
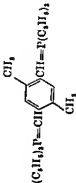
A. Monophosphoranes—Continued

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature °C.	References
C₆ (contd.)	(C₆H₅)₃P CHC≡CC₃H₇-n	NaOC₂H₅, C₂H₅OH	30 min., 20	325
	(C₆H₅)₃P CH(CH=CH)CH₂CH₃	LiC₄H₉-n, (C₂H₅)₂O	3 hr., 20	181
	(C₆H₅)₃P CHCH=C(CH₃)CH=CH	LiC₄H₉, (C₂H₅)₂O	1 hr., 20	328
		LiOC₄H₉, (C₂H₅)₂O	3 hr., 20	377
	(C₆H₅)₃P CHC(CH₃)₂·CHCH₂OCH₃	LiC₄H₉, C₆H₆		376a
	(C₆H₅)₃P CHC(CH₃)₃ CHCO₂CH₃	NaOC₂H₅, C₂H₅OH	4 min., 20	282
		NaC≡CH, DMF	2 hr., 20	55
		NaNH₂, C₆H₆	1 day, 20	55
	(C₆H₅)₃P CHCH C(CH₃)CO₂CH₃ (67)	NaOH, H₂O		232, 235
		NaOCH₃, C₆H₆Cl₂		207
	(C₆H₅)₃P C(CH₃)CH CHCO₂CH₃ (67)	NaOH, H₂O		233, 234
	(C₆H₅)₃P	LiC₄H₉-n, (C₂H₅)₂O	5–6 hr., 20	113, 185
C₇	(C₆H₅)₃P CHC₅H₁₁-n	LiC₄H₉-n, (C₂H₅)₂O	1 hr., 20	188, 189
	(C₆H₅)₃P CH(CH₂)₃CH CH₂	LiC₄H₉-n, (C₂H₅)₂O	2 hr., 20	160
	(C₆H₅)₃P CHCH CHC₄H₉-n	LiC₄H₉-n, (C₂H₅)₂O	2 hr., 20	258
	(C₆H₅)₃P CHCH=n CHC(CH₃) CHCH₃	LiC₄H₉-n, (C₂H₅)₂O	4 hr., 20	287
		NaNH₂, C₆H₆	50 hr., 20	287
		NaOCH₃, DMF		287
	(C₆H₅)₃P CHC≡CC(CH₃)₃ · CHCH₃	LiC₄H₉, (C₂H₅)₂O	2 hr., 20	209
	(C₆H₅)₃P CHCH C(CH₃)CH(OC₂H₅)₂	NaOCH₃, CH₃OH		210
	(C₆H₅)₃P CH	LiC₄H₉-n, (C₂H₅)₂O	2 hr., 20	314
		LiC₄H₉, (C₂H₅)₂O	2 hr., 20	158

$(C_6H_5)_3P=CHC_6H_5$

Reactant	Reagent	Conditions	Refs.
	$LiC_6H_5-m, (C_2H_5)_2O$	30 min., 20	41, 213
	$LiC_6H_5, (C_2H_5)_2O$	20	2, 3, 194, 209
			209
$(C_6H_5)_3P=CHC_6H_4Cl-p$	LiC_6H_5, THF	3 hr., 20	209
$(C_6H_5)_3P=CHC_6H_4Cl-2,4$	C_6H_5MgBr, THF	2 days, reflux	61
$(C_6H_5)_3P=CHC_6H_4NO_2-m$	$Na, (C_2H_5)_2O$	16 hr., 20	53
$(C_6H_5)_3P=CHC_6H_4NO_2-p$	$NaNH_2, C_6H_6$	1 day, -50	53
	$NaNH_2, liq.$		113
	$NaC \equiv CH, DMF$	20	201
	$NaOCH_3, DMF$	10 min., 20	104, 198
	$LiOCH_3, C_2H_5OH$	2 days, 20	3, 64, 213
	$NaOCH_3, C_2H_5OH$	0	113
	$NaOCH_3, DMF$		201
	$NaOH, C_2H_5OH/H_2O$		220
	$Na_2CO_3, C_2H_5OH/H_2O$		210
	$LiOC_2H_5, C_2H_5OH$		160
$(C_6H_5)_3P=CHCOC_6H_5$	$NaOC_2H_5, C_2H_5OH$	2 hr., 20	60
	$NaOH, C_2H_5OH/H_2O$		220
	$LiC_6H_5, (C_2H_5)_2O$		229
		0	248
	$LiC_6H_5-m, (C_2H_5)_2O$	20 min., 20	71
	$NaOH, H_2O$	10 min., 20	330
	$NaOCH_3, CH_2Cl_3$	0 hr., 20	236, 297
	$LiC_6H_5, (C_2H_5)_2O$	10 min., 20	290
	$LiC_6H_5-n, (C_2H_5)_2O$	12 hr., 20	183, 184
	$LiC_6H_5-i, (C_2H_5)_2O$	15 hr., 20	158
	$LiC_6H_5-m, THF/(C_2H_5)_2O$	~65	69

C₉

Note References 391 to 404 are on p. 490.

TABLE III —Continued

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES

A. Monophosphoranes —Continued

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature °C	References
C_7 (contd.)	$(C_6H_5)_3P$: $CHC_6H_4CH_3$-m	$NaOC_2H_5$, C_2H_5OH		60
	$(C_6H_5)_3P$: $CHC_6H_4CH_3$-p	$LiOC_2H_5$, C_2H_5OH		195, 196
	$(C_6H_5)_3P$: $CHC_6H_4OCH_3$-p	LiC_4H_9-n, C_6H_6	20	160
		C_6H_5MgBr, THF		113
	$(C_6H_5)_3P$: $CHOC_6H_4CH_3$-p	LiC_4H_9-n, $(C_2H_5)_2O$	5 hr., 20	248
		KOC_4H_9-t, t-C_4H_9OH	20 min., 20	248
	$(C_6H_5)_3P$: $CHC_6H_2O_2CH_3$-3,4	$NaOCH_3$, DMF	2 hr., 65	201
	$(C_6H_5)_3P$: $CHC_6H_4(HO)$-p	$NaOC_2H_5$, C_6H_5OH		398
	$(C_6H_5)_3P$: $CHOC_6H_5$ (87)	$NaOH$, H_2O		60
		Na_2CO_3, H_2O	15 hr., 20	31
	$(C_6H_5)_3P$: $CClOC_6H_5$ (87)	$NaOH$, H_2O		60
		Pyridine, $CH_3C_6H_6$	30 min., −70	60
	$(C_6H_5)_3P$: $CHClOC_6H_5$-n (81)	KOH, CH_3OH/H_2O		257
	$(C_6H_5)_3P$: $CHCH$ $CH_2CH(CH_3)CH$ CH_2	LiC_4H_9-n, $(C_2H_5)_2O$	2 hr., 20	160
	$(C_6H_5)_3P$: $CH_2CH(CH_3)CHCH_2OCOCH_3$	LiC_4H_9-n, $(C_2H_5)_2O$	10 min., 20	290
		$NaOC_2H_5$, DMF	20	
C_8	$(C_6H_5)_3P$: CH—⟨ring⟩—OCH$_3$	LiC_4H_9-n, THF/$(C_2H_5)_2O$	~25	60
	$(C_6H_5)_3P$: $CHCH$: CHC_6H_5	LiC_4H_9-n, $(C_2H_5)_2O$	30 min., 20	213
		LiC_4H_9-n, $(C_2H_5)_2O$		138
		$LiOC_4H_9$, C_2H_5OH		210, 211
		$NaOC_2H_5$, C_6H_5OH		60
		$NaOCH_3$, DMF		201
	$(C_6H_5)_3P$: $CHC_6H_4(OCH_3)_3$-2,3,4	$LiOC_4H_9$, C_2H_5OH		208
	$(C_6H_5)_3P$: $CHC_6H_3(OCH_3)(OH)$-2,4	$NaOH$, H_2O		68, 380
	$(C_6H_5)_3P$: $CHC_6H_4CO_2CH_3$			203
	$(C_6H_5)_3P$: $CHCH_2C_6OC_6H_5$	LiC_4H_9-n, $(C_2H_5)_2O$/C_6H_5		

	Structure	Base, Solvent	Time, Temp.	Refs.
(C₆H₅)₃P=CHC₃H₆CO₂CH₃-p		LiOC₂H₅, C₆H₅OH		193, 210
(C₆H₅)₃P=CHC₆H₄N(CH₃)₂-p		NaOCH₃, DMF or (CH₃)₂SO		199, 200
		LiOCH₃, C₆H₅OH		210
(C₆H₅)₃P=CH-C₆H₅		C₆H₅Li, (C₄H₉)₂O		276, 277
(C₆H₅)₃P=CH₂		LiC₄H₉, (C₂H₅)₂O	1-2 hr., 20	264, 275, 328
		NaOCH₃, DMF	10	274, 368
(C₆H₅)₃P=CH₂		NaOCH₃, CH₃OH		279
(C₆H₅)₃P=CH₂				
	OH			
(C₆H₅)₃P=CH₂		NaOCH₃, CH₃OH	1 hr., 20	279
(C₆H₅)₃P=CHCH=CHCH=CH(C=C)CH₃		LiC₄H₉, -n, (C₂H₅)₂O	1 hr., 20	241
(C₆H₅)₃P=CHCH=CHCH=CHCH₃)₂CH=CHCH₃		LiC₄H₉-n, (C₂H₅)₂O		259
(C₆H₅)₃P=CHCH		LiC₄H₉, THF	1 hr., 20	209
		LiC₄H₉, -n	3 hr., 20	328
		LiC₄H₉, (C₂H₅)₂O	1 hr., 20	209, 275, 293
		LiC₄H₉, THF		368
		Na..., DMF	1 hr., 20	113, 293
		NaOCH₃, DMF	20	274
		LiC₄H₉-n, (C₂H₅)₂O	30 min., 20	293
		LiC₄H₉-n, (C₂H₅)₂O	15 min., 20	181
				180
[(C₆H₅)₃P=CH-CH=CH-CH=CH]C₆H₅-n		LiC₄H₉, (C₂H₅)₂O		214
[(C₆H₅)₃As=CH-CH=CH(CH=C)₂C₆H₅-t]				
(C₆H₅)₃P=CHCH				
(C₆H₅)₃P=CHC₅H₇-β		NaOC₂H₅, C₂H₅OH	20	197

C₉

C₁₁

Note References 391 to 404 are on p. 490.

TABLE III—Continued

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES

A. Monophosphoranes—Continued

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C_{11} (contd.)	$(C_6H_5)_3P=CH$—[OCH$_3$]	NaOCH$_3$, CH$_3$OH		278
	$(C_6H_5)_3P=CH$—[OCH$_3$]	NaOCH$_3$, CH$_3$OH		278
	$(C_6H_5)_3P=CH(CH_2)_3COC_4H_9$	NaOC$_2$H$_5$, C$_2$H$_5$OH	20	202
	$(C_6H_5)_3P=CH(CH_2)_3CO_2C_2H_5$	NaNH$_2$, THF		170, 171
		NaOC$_2$H$_5$, THF or DMF		170, 171
	$(C_6H_5)_3P=$ [chain] CO$_2$CH$_3$	NaOCH$_3$, CH$_2$Cl$_2$		297, 298
C_{12}	$(C_6H_5)_3P=CHC_{11}H_{23}$-$n$	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	20	159
		LiC$_6$H$_5$, THF/(C$_2$H$_5$)$_2$O		113
	$(C_6H_5)_3P=$ [chain] CO$_2$C$_2$H$_5$	NaOCH$_3$, CH$_2$Cl$_2$	1 hr., 20	236
	$(C_6H_5)_3P=CHCH_2$—[dioxane]C$_6$H$_5$	LiC$_4$H$_9$-n, (C$_2$H$_5$)$_2$O	15 min., 20	72
	$(C_6H_5)_3P=CH$—[cyclohexene-O-tetrahydropyran]	LiC$_6$H$_5$, (C$_2$H$_5$)$_2$O	17 hr., 20	70

C₁₃	(C₆H₅)₃P=CH(CH₃)CO₂C₂H₅		NaNH₂, THF		170, 171
			NaOC₂H₅, THF or DMF		170, 171
	(C₆H₅)₃P=C(CH₃)CH=CH		LiC₆H₅, THF	2 hr, 20	209
			LiC₆H₅, (C₂H₅)₂O	15 min., 0	240
			C₂H₅MgBr, THF	1 hr, 20	240
			NaC≡CH, DMF	12 hr, 20	289
			NaNH₂, C₂H₅		240
			NaOCH₃, C₂H₅		240
			NaOCH₃, DMF		289
			NaOCH₃, DMF		113, 291
	(C₆H₅)₃P=C(C₆H₅)₂		NaC(C₂H₅)₃, (C₂H₅)₂O	30 min. or 3 hr, 20	64
			NaOCH₃, (C₂H₅)₂O	1 day, 20	88
	(C₆H₅)₃P=C(C₆H₄)C₆H₄C₆H₄NO₂ p		NaOC₂H₅, C₂H₅OH		44
	(C₆H₅)₃P=C(C₁₂H₈)		NH₄OH, C₂H₅OH		48
			NaOH, CHCl₃/H₂O		88
C₁₄	(C₆H₅)₃P=C(OC₂H₅)₂		LiC₆H₅, (C₂H₅)₂O		87
	(C₆H₅)₃P=C=C(C₆H₅)₂		LiC₆H₅, (C₂H₅)₂O	−40	123
C₁₅	(C₆H₅)₃P=CHCH=C(CH₃)CH₂CH		NaOCH₃, DMF	1 hr, 20	265
	(C₆H₅)₃P=CHCH=C(CH₃)CH=CH		NaOCH₃, DMF	0	264

Note. References 301 to 401 are on p. 400.

TABLE III—Continued

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES

A. Monophosphoranes—Continued

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C₁₅ (contd.)				
	$(C_6H_5)_3P$=CHCH=C(CH_3)CH	$LiC_6H_5, (C_2H_5)_2O$	20 min., 20	54, 283
		$NaC≡CH, DMF$	1 day, 20	54, 283
			2 days, —5	270
		$NaNH_2, C_6H_6$	1 day, 20	54, 283
		$NaOCH_3, CH_3OH$		285
		$NaOCH_3, DMF$		283
		$NaOC_2H_5, C_2H_5OH$	10 min., 20	54
		$NaOC_2H_5, DMF$	10 min., 20	283
		KOC_2H_{9-7}, DMF		270
		$NaOH, CH_3OH$ or C_2H_5OH, or DMF		269, 270, 204
		KOH, CH_3OH		284
	$(C_6H_5)_3P$=CHCH=C(CH_3)CH=CH	$NaOCH_3, DMF$		204
	$(C_6H_5)_3P$=CHCH=C(CH_3)CH=CH			
		$NaOC_2H_5, C_2H_5OH$		288
	$(C_6H_5)_3P$=CHC_6H_4(CH=CHC_6H_5)-p	$LiOC_2H_5, C_2H_5OH$	20	195, 196
	$(C_6H_5)_3P$=CHCH=CH(C_6H_5)_2	$LiOC_2H_5, C_2H_5OH$		211
C₁₆	$(C_6H_5)_3P$=CH-⟨⟩-CH=CHC_6H_4CH_3-p	$LiOC_2H_5, C_2H_5OH$	20	196

	Reactant	Conditions	Yield/Ref.
C₁₇	$(C_6H_5)_3P=CH$ (pyrene)	$NaOC_2H_5, C_2H_5OH$	20, 197
C₁₈	$(C_6H_5)_3P=CHCO_2C_nH_{2n+1}$	$NaOCH_3, C_2H_5OH/DMF$	270
		$NaOH, H_2O$	39
C₁₉	$(C_6H_5)_3P=[(CH_2)_3CO_2C_nH_{2n+1}]$	$NaOCH_3, CH_2Cl_2$	39 (30 min., 20)
		$NaOCH_3, CH_2Cl_2$	39 (30 min., 20)
C₂₀	$(C_6H_5)_3P=$	$LiC_4H_9-n, (C_2H_5)_2O$	267 (90 min., 20)
C₂₃	$(C_6H_5)_3P=CH$	$NaOCH_3, DMF$	206
		KOH, CH_3OH or C_2H_5OH	206
	$(C_6H_5)_3P=CH$—$CH=CH$ (phenyl)	$LiOC_2H_5, C_2H_5OH$	106, 108

TABLE III—Continued

ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES

B. Bis-phosphoranes

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, C°	References
C₂	(C₆H₅)₃P=C=P(C₆H₅)₃ (70)	K, diglyme	20 min., reflux	81
C₃	(C₆H₅)₃P=CHOCH=P(C₆H₅)₃	NaOCH₃, CH₃OH	2 hr., 20	190
C₃	(C₆H₅)₃P=CHCH₂CH=P(C₆H₅)₃	LiC₆H₅, (C₂H₅)₂O		52
		NaNH₂, liq. NH₃		52
C₄	(C₆H₅)₃P·CHCH₂CH₂CH=P(C₆H₅)₃	LiCH₃, THF	4 hr., 20	113
		LiC₄H₉-n, (C₂H₅)₂O	1 hr., 20	74
		LiC₄H₉-n, THF		299–301
		LiC₆H₅, (C₂H₅)₂O	1–2 hr., 20	74, 185
		NaNH₂, liq. NH₃		52
		NaOC₂H₅, C₂H₅OH		74
		KOC₄H₉-t, t-C₄H₉OH	1 day, 20	302
		LiC₄H₉, THF	30 min., 20	209
		LiOC₂H₅, C₂H₅OH		212
C₅	(C₆H₅)₃P=CHCH=CHCH=P(C₆H₅)₃	LiOC₂H₅, C₂H₅OH		188, 189
		LiC₄H₉-n, (C₂H₅)₂O		79
C₅	(C₆H₅)₃P=CH(CH₂)₃CH=P(C₆H₅)₃	Na₂CO₃, H₂O	2 hr., 20	201a
C₆	(C₆H₅)₃P=CHCO₂CH₂CH₂OCOCH=P(C₆H₅)₃ (67)	LiOC₂H₅, C₂H₅OH		188, 189
	o-C₆H₄[CH=P(C₆H₅)₃]₂	LiC₄H₉-n, (C₂H₅)₂O		193, 195, 210
C₆	p-C₆H₄[CH=P(C₆H₅)₃]₂	NaOC₂H₅, C₂H₅OH		66
C₁₀	(C₆H₅)₃P=CH⌇…CH=P(C₆H₅)₃	LiC₆H₅, (C₂H₅)₂O	30 min., 20	80, 271
C₁₀	(C₆H₅)₃P=CH⌇…C=C…CH=P(C₆H₅)₃	LiC₄H₉, (C₂H₅)₂O	30 min., 20	80, 271

103, 210

187

187, 196

201a

$LiOC_2H_5, C_2H_5OH$

$LiOC_2H_5, C_2H_5OH$

$LiOC_2H_5, C_2H_5OH$

$LiOC_2H_5, C_2H_5OH$

CH_3

$(C_6H_5)_3P=CH$ · · · $CH=P(C_6H_5)_3$

CH_3

C_{16}

$(C_6H_5)_3P=CH$ · · · $CH=P(C_6H_5)_3$

C_{16}

$(C_6H_5)_3P=CH$ · · · $CH=P(C_6H_5)_3$

$CH=$

C_{24}

$(C_6H_5)_3P=CH$ · · · $CH=CH$ · · · $CH=CH$

C_{26}

$(C_6H_5)_3P=CH$ · · · $CH=CH$

Note. References 391 to 401 are on p. 400.

TABLE IV

ALKYLIDENE PHOSPHORANES PREPARED FROM YLIDES

Carbon Atoms in Alkylidene Group	Phosphorane	Reactants (Solvent, Time, Temperature, °C.)	Yield, %	References
C_3	$(C_6H_5)_3P{=}CHCHO$	$(C_6H_5)_3P{=}CH_2 + HCO_2C_2H_5$	67	33
	$(C_6H_5)_3P{=}CClCHO$	$(C_6H_5)_3P{=}CHCHO + C_6H_5ICl_2$	66	59
	$(C_6H_5)_3P{=}CBrCHO$	$(C_6H_5)_3P{=}CHCHO + Br_2$	83	59
	$(C_6H_5)_3P{=}C(CH_3)CHO$	$(C_6H_5)_3P{=}CHCH_3 + HCO_2C_2H_5$	—	33
	$(C_6H_5)_3P{=}CHCOCH_3$	$(C_6H_5)_3P{=}CH_2 + CH_3COSC_2H_5$	78	32
	$(C_6H_5)_3P{=}CClCOCH_3$	$(C_6H_5)_3P{=}CHCOCH_3 + Cl_2(CH_2Cl_2/pyridine, -70)$	46	60
C_3	$(C_6H_5)_3P{=}CBrCOCH_3$	$(C_6H_5)_3P{=}CHCOCH_3 + C_6H_5ICl_2$	88	59
	$(C_6H_5)_3P{=}CHCO_2CH_3$	$(C_6H_5)_3P{=}CHCOCH_3 + Br_2$	87	59
	$(C_6H_5)_3P{=}CClCO_2CH_3$	$(C_6H_5)_3P{=}CH_2 + ClCO_2CH_3$	80	111
		$(C_6H_5)_3P{=}CHCO_2CH_3 + C_6H_5ICl_2$ $(C_6I_6, 30 \text{ min.}, 10)$	95	117
	$(C_6H_5)_3P{=}CBrCO_2CH_3$	$(C_6H_5)_3P{=}CHCO_2CH_3 + Br_2 (C_6H_6)$	96	59
		$(C_6H_5)_3P{=}CHCO_2CH_3 + I_2 (CH_3OH)$	87	117
	$(C_6H_5)_3P{=}CClCOC_2H_5$	$(C_6H_5)_3P{=}CHCOC_2H_5 + C_6H_5ICl_2$	94	59
	$(C_6H_5)_3P{=}CBrCOC_2H_5$	$(C_6H_5)_3P{=}CHCOC_2H_5 + Br_2$	97	111
	$(C_6H_5)_3P{=}CClCO_2C_2H_5$	$(C_6H_5)_3P{=}CHCl_3 + ClCO_2CH_3$	95	60
		$(C_6H_5)_3P{=}CHCO_2C_2H_5 + Cl_2$ $(CH_2Cl_2/(C_2H_5)_3N, -70)$	80	60
	$(C_6H_5)_3P{=}CBrCO_2C_2H_5$	$(C_6H_5)_3P{=}CHCO_2C_2H_5 + Br_2$ $(CH_2Cl_2/NaOH, -70)$	69	60
C_5	$(C_6H_5)_3P{=}C(CO_2CH_3)C_2H_5$	$(C_6H_5)_3P{=}CHCO_2C_2H_5 + ClCO_2CH_3$	88	111
	$(C_6H_5)_3P{=}C(COCH_3)CO_2CH_3$	$(C_6H_5)_3P{=}CHCO_2C_2H_5 + CH_3COCl$ $(C_6H_6, 3 \text{ hr}, 20)$	97	331
	$(C_6H_5)_3P{=}C(CH_2CN)CO_2CH_3$	$(C_6H_5)_3P{=}CHCO_2C_2H_5 + BrCH_2CN$ $(CH_3CO_2C_2H_5, 4-5 \text{ hr, reflux})$	80	40
C_6	$(C_6H_5)_3P{=}C(COCH_2)C_3H_7{-}n$	$(C_6H_5)_3P{=}CHCH_2{-}n + CH_3COSC_2H_5$	62	32
	$(C_6H_5)_3P{=}C(COC_3H_7{-}n)CH_3$	$(C_6H_5)_3P{=}CHCl_3{-}n + n{-}C_3H_7COSC_2H_5$	54	32
	$(C_6H_5)_3P{=}C(CO_2CH_2)C_3H_7{-}n$	$(C_6H_5)_3P{=}CHCH_2{-}n + ClCO_2CH_3$	96	111
	$(C_6H_5)_3P{=}C(CH_2CH{=}CH_2)CO_2CH_3$	$(C_6H_5)_3P{=}CHCO_2CH_3 + CH_2{=}CHCH_2Br$ $(CH_3CO_2C_2H_5, 4-5 \text{ hr, reflux})$	93	40
C_6	$(C_6H_5)_3P{=}C(COC_3H_7{-}n)CN$	$(C_6H_5)_3P{=}CHCN + n{-}C_3H_7COCl$	81	330
	$(C_6H_5)_3P{=}C(CH_2CO_2CH_3)CO_2CH_3$	$(C_6H_5)_3P{=}CHCO_2CH_3 + BrCH_2CO_2CH_3$ $(CH_3CO_2C_2H_5, 4-5 \text{ hr, reflux})$	98	40

	Yield (%)	Reference
C₈		
$(C_6H_5)_3P=C(COOC_2H_5)\cdot n\text{-}C_3H_7$ $(C_6H_5)_3P=CHCH_3, n + n\text{-}C_3H_7COCl$		330
$(C_6H_5)_3P=C(COC_2H_5)\cdot NO_2\text{-}p$ $(C_6H_5)_3P=CHCl + C_6H_5COCl$	—	32
$(C_6H_5)_3P=CHCl + C_6H_5COSC_2H_5$	63	32
$(C_6H_5)_3P=CHCl + C_6H_5COSC_2H_5$	80	32
$(C_6H_5)_3P=CHCl + Cl_3$	93	60
$(CH_3)_3P(pyridine, -70)$	92	
$(C_6H_5)_3P=CHCOC_6H_5, \; 3 \; \text{hr, min, } -70)$	93	60
$(C_6H_5)_3P=CHCOC_6H_5 + i\text{-}C_4H_9ICl_3$		59
$(CCl_3C)_3/KOH, -70)$	87	60
$(C_6H_5)_3P=CCl\cdot COC_2H_5 + n\text{-}C_3H_7COCl$	91	330
$(C_6H_5)_3P=CHCl\cdot CH=CHCOCl$	84	329, 330
$(C_6H_5)_3P=CHCOC_6H_5, + C_6H_5COCl$ [furan]	57	331
C₉		
$(C_6H_5)_3P=CHCOCH_3$	Quant.	
$(C_6H_5)_3P=CHCOC_6H_5$		
$(C_6H_5)_3P=CHCOCH_3, \; 3 \; \text{hr, } 20)$	42	32
$(C_6H_5)_3P=CHCOCH_3 + C_6H_5CH_2COSC_2H_5$	68	32
$(C_6H_5)_3P=CHCOCH_3 + C_6H_5COSC_2H_5$	93	32
$(C_6H_5)_3P=CHCl + C_6H_5COSC_2H_5$		111
$(C_6H_5)_3P=CHCl + Cl(CO)_2C_2H_5$	68	329, 330
$(C_6H_5)_3P=CHCOC_6H_5, \; 2 \; \text{hr, } 20)$		
$CH_3CH=CHCH=CHCOCl$	74	330
$(C_6H_5)_3P=CH_2 + C_6H_5CH_2CH_2COSC_2H_5 +$ $C_6H_5CH_2CH_2COCl$	80	32
$(C_6H_5)_3P=CH_2 + o\text{-}ClC_6H_4\cdot$ (reflux)	75	40
$(C_6H_5)_3P=CHCOC_6H_5 + C_6H_5COCl$	83	32, 331
$(C_6H_5)_3P=CHCOC_6H_5, \; 3 \; \text{hr, } 20)$	Quant.	
$(C_6H_5)_3P=CHCOCH_3 + o\text{-}ClC_6H_4COCl$		331
C₁₀		
$(C_6H_5)_3P=CHCOCH_3 + p\text{-}ClC_6H_4COCl$	98	331
$(C_6H_5)_3P=CHCOCH_3 + m\text{-}O_2NC_6H_4COCl$	98	331

TABLE IV—*Continued*

ALKYLIDENE PHOSPHORANES PREPARED FROM YLIDES

Carbon Atoms in Alkylidene Group	Phosphorane	Reactants (Solvent, Time, Temperature, °C.)	Yield, %	References
C$_{11}$	(C$_6$H$_5$)$_3$P=CCH$_3$ | COCH$_2$CH$_2$C$_6$H$_5$	(C$_6$H$_5$)$_3$P=CHCH$_3$ + C$_6$H$_5$CH$_2$CH$_2$COSC$_2$H$_5$	70	32
	(C$_6$H$_5$)$_3$P=C(OCH$_2$CH$_2$C$_6$H$_5$)CH$_3$	(C$_6$H$_5$)$_3$P=CHCH$_3$ + C$_6$H$_5$CH=CHCOSC$_2$H$_5$	70	32
	(C$_6$H$_5$)$_3$P=C(COCH$_2$CH$_2$C$_6$H$_5$)CO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + C$_6$H$_5$CH$_2$CH$_2$COCl (C$_6$H$_6$, 3 hr., 20)	77	331
	(C$_6$H$_5$)$_3$P=C(COC$_6$H$_4$(CH$_3$-p)CO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + p-CH$_3$C$_6$H$_4$COCl (C$_6$H$_6$, 3 hr., 20)	95	331
	(C$_6$H$_5$)$_3$P=C(COC$_6$H$_4$(OCH$_3$-o)CO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + o-CH$_3$OC$_6$H$_4$COCl (C$_6$H$_6$, 3 hr., 20)	Quant.	331
	(C$_6$H$_5$)$_3$P=C(COC$_6$H$_4$(OCH$_3$-m)CO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + m-CH$_3$OC$_6$H$_4$COCl (C$_6$H$_6$, 3 hr., 20)	Quant.	331
C$_{12}$	(C$_6$H$_5$)$_3$P=C(CH$_2$CH=CHC$_6$H$_5$)CO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + C$_6$H$_5$CH=CHCH$_2$Br (CH$_3$CO$_2$C$_2$H$_5$, 4–5 hr., reflux)	81	40
	(C$_6$H$_5$)$_3$P=CCO$_2$CH$_3$	(C$_6$H$_5$)$_2$P=CHCO$_2$CH$_3$ + C$_6$H$_5$CH=CHCOCl (C$_6$H$_6$, 3 hr., 20)	Quant.	331
C$_{13}$	(C$_6$H$_5$)$_3$P=C COCH=CHC$_6$H$_5$ / C$_3$H$_7$-n	(C$_6$H$_5$)$_3$P=CHC$_3$H$_7$-n + C$_6$H$_5$CH$_2$CH$_2$COSC$_2$H$_5$	63	32
C$_{14}$	(C$_6$H$_5$)$_2$P=C(COCH$_2$CH$_2$C$_6$H$_5$)C$_6$H$_5$	(C$_6$H$_5$)$_2$P=CHC$_6$H$_5$ + C$_6$H$_5$COSC$_2$H$_5$	58	32
	(C$_6$H$_5$)$_3$P=C(COC$_{10}$H$_7$-α)CO$_2$CH$_3$	(C$_6$H$_5$)$_3$P=CHCO$_2$CH$_3$ + α-C$_{10}$H$_7$COCl	78	331

Note: References 301 to 401 are on p. 496.

TABLE V

ALKYLIDENE PHOSPHORANES PREPARED DIRECTLY FROM TRIPHENYLPHOSPHINE

Alkylidenephosphorane	Reagents: $(C_6H_5)_3P$ and	Solvent, Time, Temperature, °C.	References
$(C_6H_5)_3P=CH_2$	$CH_2N_2 + Cu^+$	THF	90
$(C_6H_5)_3P=CHCl$	$CH_2Cl_2 + LiC_4H_9\text{-}n$	-60	91, 92
			95, 96
$(C_6H_5)_3P=CF_2$	CF_2Cl_2 or CF_2Br_2	$(C_2H_5)_2O, -30$	98
$(C_6H_5)_3P=CCl_2$	$CHCl_3 + KOC_4H_9\text{-}t$		93
	CCl_4	Pentane, 0–5	94
$(C_6H_5)_3P=CBr_2$	$CHBr_3 + KOC_4H_9\text{-}t$	Heptane, 0	98
	CBr_4	2 hr, 60	94
		Heptane, 0	94
		CH_2Cl_2	82
[cyclohexadienone phosphorane structure]	$C_6H_5 \cdot CHN_2 + Cu^+$	C_6H_6, 20 hr, 20	99
[cyclohexadienone phosphorane structure with OH]	$C_6H_5 \cdot CH=CHClC_6H_5$	THF	90
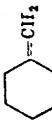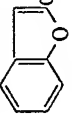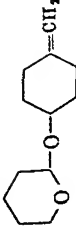
Note: References 391 to 404 are on p. 490.

TABLE VI

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials

Ylide: $(C_6H_5)_3P\sim CH_2$

Product	Yield, %	Solvent, Time, Temperature, °C.	References
n-C₄H₉OCH=CH₂		$(C_2H_5)_2O$, 12 hr, 20; 3 hr, reflux	113
n-C₄H₉C(CH₃)=CH₂	12	$(C_2H_5)_2O$, 4 hr, 60–75	182
(methylenecyclohexane) =CH₂	52	$(C_2H_5)_2O$, 3 hr, 65	2
(methylenecycloheptane) =CH₂	5–10		173
C₆H₅CH=CH₂	67	$(C_2H_5)_2O$, 1 hr, 20; 12 hr, 65	2
(N-ring) =CH₂	63	$(C_2H_5)_2O$, 6 hr, reflux; 2 days, 20	322
(CH₃)₂C=CHCH₂CH₂C(CH₃)=CH₂	10	$(C_2H_5)_2O$, 4 hr, 60–75	182
CH₂=C(CH₃)(CH₂)₃C(CH₃)=CH₂	11	$(C_2H_5)_2O$, 4 hr, 60–75	182
(methylenecyclooctane) =CH₂	74	$(C_2H_5)_2O$, 3 hr, 65	173
C₆H₅C(CH₃)=CH₂		$(C_2H_5)_2O$, 3 hr, 65	2
n-C₇H₁₅C(CH₃)=CH₂	69	$(C_2H_5)_2O$, 1 hr, 20; 5 hr, 65	401
C₆H₅CH–CHCH=CH₂	75	$(C_2H_5)_2O$, 2 hr, reflux	2
o-C₆H₄(CH=CH₂)₂			52
(t-C₄H₉)₂CHCH=CH₂	70	$(C_2H_5)_2O$/THF, 12 hr, 20	402
(benzofuran) C(CH₃)=CH₂		THF, 90 min, reflux	324
(cyclohexyl–O–tetrahydropyran) =CH₂		$(C_2H_5)_2O$, 1 hr, 20; 2 hr, 65	70

	53	(C₂H₅)₂O, 40 hr., 20	174
	61	(C₂H₅)₂O, 40 hr., 20	174
	22	(C₂H₅)₂O, 70 hr., 60	171
	61	(C₂H₅)₂O, 1 day, 60	323
$p\text{-}O_2NC_6H_4C(C_6H_5){=}CH_2$	54 62	(C₂H₅)₂O, 20 CH₃OCH₂CH₂OCH₃, 4 hr., reflux	1 90
	62	(C₂H₅)₂O, 3 hr., 65	2
	6	(C₂H₅)₂O, 26 hr., 65 THF, 7 hr., 20	139, 185 310, 211

TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. *Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_9 $(C_6H_5)_3P=CH_2$ *(contd.)*			$(C_2H_5)_2O$, 12 hr., 20	183
			THF	176
		14	$(C_2H_5)_2O$, 3 hr., 65	308, 309
	$(C_6H_5)_2C=CHCH=CHCH=CH_2$ $CH=CH_2$	54	$(C_2H_5)_2O$, 5 hr., 20; 12 hr., 45	138
			$(C_2H_5)_2O$, 12 hr., 65	180
	$[p\text{-}(CH_3)_2NC_6H_4]_2C=CH_2$	90	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 65	2
		84	THF, 38 hr., reflux	175

$CH_3CHCH_2CH_2CH_2CH_2C(CH_3)_2$—$CH_3$
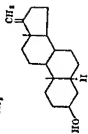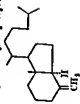
67	$(C_2H_5)_2O$, 1.5 hr., 20; 3.5 hr., 65	317
59	THF, 6 hr., reflux	254
35	THF, 6 hr., reflux	254
35	THF, 6 hr., reflux	254
57	THF, 6 hr., reflux	254
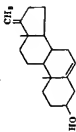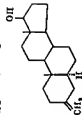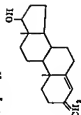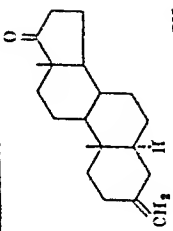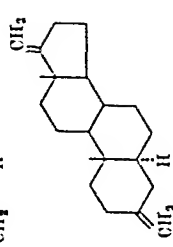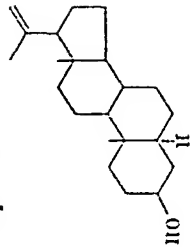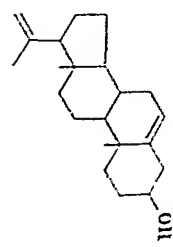
References 391 to 404 are on p. 400.

TABLE VI—*Continued*

Olefins Prepared by the Wittig Reaction
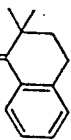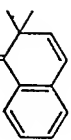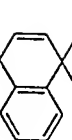
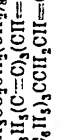*A. Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_1 $(C_6H_5)_3P=CH_2$ (*contd.*)		55	THF, 6 hr., reflux	252
		70	THF, 6 hr., reflux	252
		55	THF, 6 hr., reflux	252
		35	THF, 6 hr., reflux	254, 400
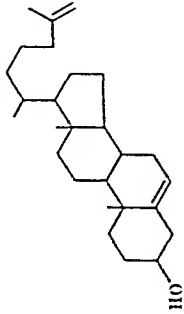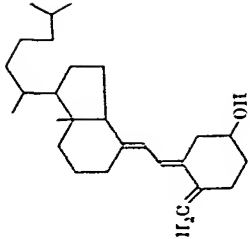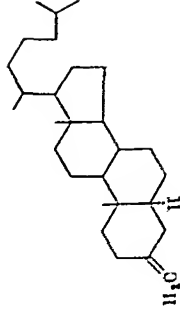
438

400		
252	THF, 6 hr., reflux	75
252	THF, 6 hr., reflux	17
252	THF, 6 hr., reflux	20
254	THF, 6 hr., reflux	48

439

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_1 $(C_6H_5)_3P\cdot CH_2$ (contd.)				
$(C_6H_5)_3PCCH_2CH(CH_3)C(CH_3)=CH_2$		71	$(C_2H_5)_2O$, 8 hr., 60	2
		53	$(C_2H_5)_2O$, 1 hr., 20; 5 hr., 65	304a, 398
		55	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., reflux	310
		60	$(C_2H_5)_2O$, 12 hr., reflux THF, 6 hr., reflux	303, 254

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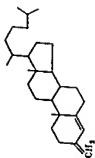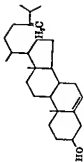
	80	THF, 6 hr., reflux	254
	69	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 65	304
	40	THF, 6 hr., reflux	254
	51	THF, 6 hr., reflux	254
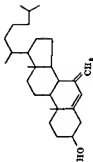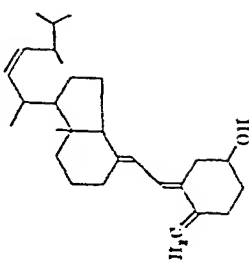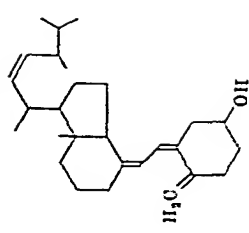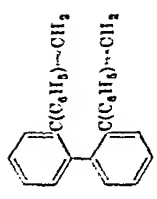
TABLE VI—Continued

Olefins Prepared by the Wittig Reaction

A. Mono-ylides as Starting Materials—Continued

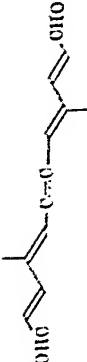| Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₅ (C₆H₅)₃P=CH₂ (contd.)		45	(C₂H₅)₂O, 1 hr., 20; 3 hr., reflux	310
			THF, 7 hr., 20	310, 311
		80	(C₂H₅)₂O, 3 days, 20	101

	THF, 6 hr., reflux	54	252
	THF, 6 hr., reflux	51	252
	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 65	71	304a
	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., reflux	65	310

CH_3CO_2

H_3C CH_3

CH_3

CH_3CO_2

H_3C COOCH$_3$

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TABLE VI *Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. Monoylidenes Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C	References
$(C_6H_5)_3P=CH(vinyl)$		51	$(C_2H_5)_2O$, 90 min., 30; 18 hrs.	313
				393
		53	$(C_2H_5)_2O$	313

	Yield (%)	Conditions	Refs.
$(C_2H_5)_3P=CF_2$, $(C_2H_5)_3P=CHCl$	20, 27	THF, 6 hr., reflux	95, 95
$C_2H_5CH=CF_2$ $(C_2H_5)_3P=C(CF_3)=CHCl$ $i-C_3H_7(CF_3)=CHCl$	30	THF, 6 hr., reflux	96
(cyclohexylidene)—CHCl	46, 29	THF, 6 hr., reflux $(C_2H_5)_2O$, −50; 3 days, 20	01,02
$(C_6H_5)_3P=CFCl$ $C_2H_5CH=CFCl$	40	Heptane, 30 min., 40–50; 2 days, 20	94
$(C_6H_5)_3P=CCl_2$ $C_6H_5CH=CCl_2$	33	Heptane, 30 min., 40–50; 2 days, 20	91
$2,6-Cl_2C_6H_3CH=CCl_2$	45	Heptane, 30 min., 40–50; 2 days, 20	91
$3,4-Cl_2C_6H_3CH=CCl_2$	72	Heptane, 30 min., 40–50; 2 days, 20	94
$p-ClC_6H_4N:C_6H_4CH=CCl_2$	43	Heptane, 30 min., 40–50; 2 days, 20	91
$p-O_2NC_6H_4CH=CCl_2$	51	Heptane, 30 min., 40–50; 2 days, 20	94
$C_6H_5C_6H_4CH=CClCH=CCl_2$	83	Heptane, 30 min., 40–50; 2 days, 20	91
$n-C_5H_{11}CH=CCl_2$	77	Heptane, 30 min., 40–50; 2 days, 20	91
$C_6H_5C=CCl_2$	20	Heptane, 30 min., 40–50; 2 days, 20	91
(terpenyl) $CH=CHCCl(CH_3)=CHBr$	59	Heptane, 30 min., 40–50; 2 days, 20	91
	46, 78	Pentane/$(C_2H_5)_2O$ CCl_4, 4 hr., 60	93, 95
$(C_6H_5)_3P=CHBr$ $C_6H_5CH=CHBr$	70	$(C_2H_5)_2O$	84
$(C_2H_5)_3P=CBr_2$ $C_6H_5CH=CBr_2$	42	Heptane, 30 min., 40–50; 2 days, 20	84
	84, 9	CH_2Cl_2 Heptane, 30 min., 40–50; 2 days, 20	82, 91

Note: References 391 to 404 are on p. 500.

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION
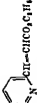
A. *Mono-ylides as Starting Materials—Continued*
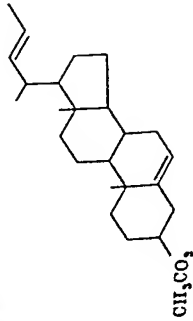
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₅ (C₄H₉)₂P=CHCH₃	CH₃O₂CC(CH₃)=CHCH₃	21	(C₂H₅)₂O, 12 hr., reflux	164
	i-C₃H₇C(CH₃)=CHCH₃		(C₂H₅)₂O, 1 hr., 20; 3 hr., 65	300
	[structure with CHCH₃]		(C₂H₅)₂O, 46 hr., 20	174
	[structure with CHCH₃]	70	(C₂H₅)₂O, 7 days, 20	174
	[structure with CHCH₃]	51	(C₂H₅)₂O, 50 hr., 60	174
	(C₄H₉)₂C=CHCH₃	98	(CH₃)₂SO, 3 hr., 25	62
	CH₃CO₂CH₂(CH₂)₈CH=CHCH=CHCH₃	07	(C₂H₅)₂O, 0	327
	C₆H₅(C≡C)₃(CH=CH)₂CH₃	5	(C₂H₅)₂O, 1 hr., reflux	261
	(C₆H₅)₃CCH₂CH=CHCH₃	58	(C₂H₅)₂O, 3 hr., 00	178
	[steroid structure with CH₃CO₂]		(C₂H₅)₂O, 1 hr., 20; 15 hr., 65	378

307

306

248

245

246, 245

247
92
92
248

$(C_2H_5)_2O$, 1 hr, 20; 5 hr, 45

$(C_2H_5)_2O$, 1 hr, 20; 15 hr, 65

$(C_2H_5)_2O$, 5 hr, 20; 15 hr, 50   57

$(C_2H_5)_2O$, −40; 30 hr, 20   15

$(C_2H_5)_2O$, −20; 15 hr, 20   71

$(C_2H_5)_2O$, 2 hr, 20   40

THF, 20   61

C_2H_5OH, 5 hr, 65   62

C_2H_5OH, 15 hr, 50   62

CH_3O, H

CH_3CO_2

CH_3, H

$(C_7H_{15})P=CHOCH_3$

$(C_5H_9)_2O-CHOCH_3$

$CHOCH_3$

$C_5H_{11}CH=CHOCH_3$

$CHOCH_3$

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TABLE VI—Continued

Olefins Prepared by the Wittig Reaction

A. Mono-ylides as Starting Materials—Continued
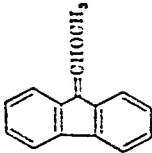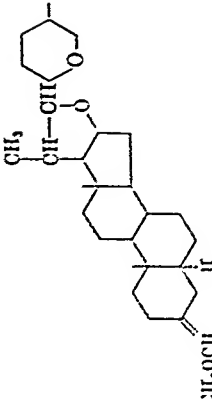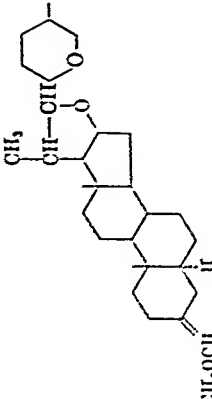
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₅ (C₆H₅)₃P=CHOCH₃ (contd.)	C₆H₅C(CH₃)=CHOCH₃	40	(C₂H₅)₂O	240
	C₆H₅CH=CHCH=CHOCH₃	50	C₂H₅OH, 1 day, 50	92
	o-C₆H₄(CH=CHOCH₃)₂	55	C₂H₅OH, 60 hr., 50	92
	(C₆H₅)₃C—CHOCH₃	83	(C₂H₅)₂O, 2 hr., 20	92, 247
		60	CH₃OH, 53 hr., 50	92
		85	(C₂H₅)₂O	240
(C₆H₅)₃P=CHSCH₃	C₆H₅CH=CHSCH₃	70	THF/(C₂H₅)₂O, 60 hr., 55	92
	(C₆H₅)₃C—CHSCH₃	84	(C₂H₅)₂O, 40 hr., 20	92
	n-C₆H₁₃CH=CHCHO	81	C₆H₆, 1 day, reflux	33, 58
(C₆H₅)₃P=CHCHO	C₆H₅CH=CHCHO	60	C₆H₆, 1 day, reflux	58, 33, 58
		15	C₆H₆, 10 hr., reflux	33, 58

456

(C₂H₅)₂P—CHCHO	C₂H₅, 20 hr., reflux	69
(C₂H₅)₂P—CHCHO	C₂H₅, 43 hr., reflux	59
(C₆H₅)₃P=CHCOONH₂	C₂H₅OH	240
		55
(C₆H₅)₃P=CHCN	C₂H₅, 20 hr., reflux	113

C_8

	C₂H₅, 50 hr., reflux	43
C₆H₅.CH=CHCHO	C₂H₅OH, 2 days, 20	84
C₆H₅.CH=CH—CHCHO		
CH₃.CH=CHCH=CHCOONH₂		
C₆H₅.CH=CHCOONH₂		
C₆H₅.CH=CHCN		
C₆H₅.CH₂.CH=CHCN		

o-O₂N.C₆H₄.CH=CHCN	C₂H₅, 4 hr., reflux	73
p-CH₃.C₆H₄.CH=CHCN	C₂H₅, 4 hr., reflux	78
m-O₂N.C₆H₄.CH=CHCN	C₆H₅, 6-10 hr., 50-60	71
2,4,6-(CH₃)₃C₆H₂.CH=CHCN	C₆H₅, 6-10 hr., 50-60	71
p-CH₃.OC₆H₄.CH=CHCN	C₆H₅, 6-10 hr., 50-60	71
3-CH₃.4-HO.C₆H₃.CH=CHCN	C₂H₅, 4 hr., reflux	85
3,4-(CH₃O)₂C₆H₃.CH=CHCN	C₂H₅, 4 hr., reflux	82
2,3,4-(CH₃O)₃C₆H₂.CH=CHCN	C₂H₅, 4 hr., reflux	82
3,4,5-(CH₃O)₃C₆H₂.CH=CHCN	C₂H₅, 4 hr., reflux	90
C₆H₅.CH=CHCO.CH₃	C₆H₅, 4 hr., reflux	
(o-C₆H₄)₂CHCl.CH=C(CH₃)₂	(C₂H₅)₂O, 12 hr., 20	64
(C₆H₅)₃C—COC₂H₅	(C₂H₅)₂O, 12 hr., 20	76
(C₂H₅)₃C—CO.CN	(C₂H₅)₂O, 1 hr., 20	61
2,4,6-Cl₃C₆H₂	None, 30 min., 145–150	

(C₆H₅)₃P=CH—CO—CH=C(CH₃)₂	None, 30 min., 145–160	50
(C₆H₅)₃P=CH—C(CH₃)₃	(C₂H₅)₂O	65

(C₂H₅)₂P—CH₂.CH—C₆H₅	(C₂H₅)₂O, 1 hr., 20; 6 hr., 65	305
(C₂H₅)₃P=C(CH₃)₃		

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued
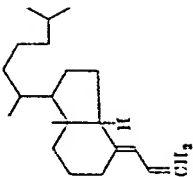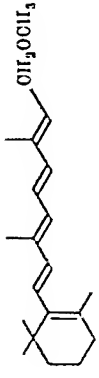
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₃ (*contd.*)				
$(C_6H_5)_3P=CHCH=CH_2$	$HC\equiv CCH=CHCH=CH_2$	53	$(C_2H_5)_2O$, 2 hr, 20	170
	$C_4H_6CH=CHCH=CH_2$	20	$(C_2H_5)_2O$, 2 hr, 20; 2 hr, 65	2
	$C_4H_5N(CH_3)CH=CHCH=CH_2$		$(C_2H_5)_2O$, 2 hr, 20; 2 hr, 65	255
	$CH_3CH=CHC=C)_2(CH=CH)_2CH=CH_2$	50	$(C_2H_5)_2O$, 2 hr, 20	250
			$(C_2H_5)_2O$, 2 days, 20	318
$(C_6H_5)_3P=CHCH_2CH_2O^{\ominus}$	$C_6H_5CH=CHCH_2CH_2OH$	65	$(C_2H_5)_2O$	10
$(C_6H_5)_3P=CHCH_2OCH_3$		10	$(C_2H_5)_2O$, 5–6 hr, reflux	281
$(C_6H_5)_3P=C(CH_3)CHO$	$n\text{-}C_6H_5CH=C(CH_3)CHO$	72	C_6H_6, 1 day, reflux	33, 68
	$C_6H_5CH=C(CH_3)CHO$	60	C_6H_6, 1 day, reflux	33, 68
$(C_6H_5)_3P=CHCOCH_3$	$(CF_3)_2C=CHCOCH_3$	93	$(C_2H_5)_2O$	210
	$C_6H_5CH=CHCOCH_3$	70	C_6H_6, 3 days, reflux	32
			THF, 2 days, reflux	31
	$m\text{-}O_2NC_6H_4CH=CHCOCH_3$	80	C_6H_6, 0–10 hr, 50–60	42
	$p\text{-}O_2NC_6H_4CH=CHCOCH_3$	92	C_6H_6, 0–10 hr, 50–60	42
	$2,4,6\text{-}(O_2N)_3C_6H_2CH=CHCOCH_3$	78	C_6H_6, 0–10 hr, 50–60	42

Reactants	Product	Conditions	Yield (%)	Refs.
$(C_6H_5)_3P=CHCOCH_3$		THF, 36 hr, reflux		401
$(C_6H_5)_3P=CHCO_2CH_3$	$C_6H_5CH=CHCOCH_3$	None, 30 hr, 90–95	95	60
$(C_6H_5)_3P=CHCO_2C_2H_5$	$CO_2N_2H_4CH=CHCOCH_3$	C_6H_6, 35 min, reflux	45	59
	$CH(OCH_3)_2CH=CHCO_2CH_3$	C_6H_6, 8 hr, reflux	59	59
		None, 90 min, 80–90	83	225, 226
		None, 150	30	35
	$o\text{-}O_2NC_6H_4CH=CHCO_2CH_3$	C_6H_6, 4 hr, reflux		162
	$m\text{-}O_2NC_6H_4CH=CHCO_2CH_3$	C_6H_6, 10 hr, reflux		162
	$p\text{-}O_2NC_6H_4CH=CHCO_2CH_3$	C_6H_6, 10 hr, reflux		162
	$2,4,6\text{-}(O_2N)_3C_6H_2CH=CHCO_2CH_3$	C_6H_6, 10 hr, reflux		162
		CH_2Cl_2, 8 hr, 20	93	227
	$o\text{-}O_2NC_6H_4CH=CHCH=CHCO_2CH_3$	C_6H_6, 10 hr, reflux		162
	$CH_3O_2CCH_2CH=CHCO_2CH_3$	C_6H_6, 5 hr, reflux	95	181, 227
		CH_2Cl_2, 12 hr, 20	85	227
	$OCH_2C(=CH_2)CH=CHCO_2CH_3$ / $CH(OCH_3)_2$	C_2H_5O, 1 day, reflux	60	237

Note References 391 to 404 are on p. 490

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Monoylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_3 $(C_6H_5)_3P$=$CHCO_2CH_3$ *(contd.)*	*(structure)*		Xylene, reflux	30
			None, 150	30
	(structure)		CH_2Cl_2, 5 hr., reflux	208
	(structure)	80	CH_2Cl_2, 5 hr., reflux	251
			C_6H_6, 6 hr., reflux	30
	(structure)		CH_2Cl_2, 5 hr., reflux	251
	(structure)		CH_2Cl_2, 5 hr., reflux	205–207
	(structure)		CH_2Cl_2, 5 hr., reflux	205–207

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				235–237
	CCl₂CH=CHCO₂CH₃	CH₂Cl₂, 3 hr, reflux		117
	CCl=C(Cl)=CHCO₂CH₃	C₆H₆, 3 hr, reflux	72	117
	CCl=C(Cl)=ClCO₂CH₃	C₆H₆, 3 hr, reflux	79	117
(C₆H₅)₃P=CHCO₂CH₃	C₆H₅CH=CHCO₂CH₃	C₆H₆, 3 hr, reflux	93	117
	=HOCH₂CH=CHCO₂CH₃	C₆H₆, 3 hr, reflux	77	117
	CH₂CH=CHClCO₂CH₃	C₆H₆, 3 hr, reflux	61	117
	CH₃CH=CHCl=CHCO₂CH₃	C₆H₆, 3 hr, reflux	94	117
		C₆H₆, 3 hr, reflux	84	117
		C₆H₆, 3 hr, reflux	78	117

	=C(CH₃)CH=CHCO₂C₂H₅	C₆H₆, 3 hr, reflux	71	117
(C₆H₅)₃P=CHCO₂C₂H₅	CH₂CH=CHClCO₂C₂H₅	C₆H₆, 3 hr, reflux	64	117
	=HOCH₂CH=CHCO₂C₂H₅	C₆H₆, 3 hr, reflux	Quant.	117
	=HOₓCH=CHCO₂C₂H₅	C₆H₆, 4 hr, 60–75	20	182

	O CH–CHCO₂CH₃ (furyl)	(C₂H₅)₂O		130
(C₆H₅)₃P=CH-C₆H₅-n	C₆H₅CH=CHCO₂CH₃			
	(CH₃)₂C=CHCO₂C₁₁H₂₃-n			

C₆

(C₆H₅)₃P=CHCH₃)₂Br	C₆N₃CH=CHCH₃)₂Br	Pet. ether, 1 hr, –20; 3 hr, 0; 3 hr, 20	72	161, 327
(C₆H₅)₃P=CHCH₃	HC≡CCH=CHCl=CHCH₃	(C₂H₅)₂O, 3 days, 20	74	74
	CH₂CH=CHCH₃	(C₂H₅)₂O, 3 hr, 20		399
	CH₃CH(CH₃)CH=CHCH–CH=CH₂	(C₂H₅)₂O, 0.1 hr, 20	50	71
	CH₃(CH₂CH₃)CH=C(CH₃)CH₂=CH₂C₂H₅	(C₂H₅)₂O, 0, 0	65	328
		(C₂H₅)₂O, 4 hr, 0; 3 hr, 20	69	328
		(C₂H₅)₂O/0THF, 30 min, 20		181

Note: References 391 to 404 are on p. 490.

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TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₄ *(cont'd.)*				
$(C_2H_5)_3P=CHC(CH_3)=CH_2$	$i\text{-}C_3H_7CH=CHC(CH_3)=CH_2$		THF, 4 hr., reflux	394
$(C_4H_5)_3P=CHC(CH_3)=CH_2$	[cyclohexylidene]—CHC(CH₃)=CH₂		THF, 4 hr., reflux	304
$(C_6H_5)_3P=CClCOC_2H_5$	$CCl_2=CClCH=CClCOC_2H_5$	53	C₆H₆, 8 hr., reflux	50
	$CCl_3=CClCH=CHCOC_2H_5$	87	C₆H₆, 8 hr., reflux	50
$(C_6H_5)_3P=CHCOC_2H_5$	$C_2H_5CH=CHCO_2C_2H_5$	40	C₆H₆, 0 hr., reflux	220
$(C_6H_5)_3P=CHCO_2C_2H_5$	$(CH_3)_2C=CHCO_2C_2H_5$	45	None, 1 day, 100	35, 218
	$CH_2F\cdot C(CH_3)=CHCO_2C_2H_5$	65	C₆H₆, 0 hr., reflux	220
	$CH_3CHBrCH=CHCO_2C_2H_5$	34	C₆H₆, 0 hr., reflux	220
	$CH_3=CHOH=CHCO_2C_2H_5$	42	None, 1 day, 100	35
	$C_2H_5C(CH_3)=CHCO_2C_2H_5$	80	C₆H₆, 0 hr., reflux	220
	$C_2H_5OCH_2CH_2CH=CHCO_2C_2H_5$	50	C₆H₆, 6 hr., reflux	220
	[cyclopentyl]—CHCO₂C₂H₅	43	None, 10 hr, 170	35
	[furanyl]CH=CHCO₂C₂H₅	51	C₆H₆, 0 hr., reflux	220
	[cyclopropane structure with CHCO₂C₂H₅, C(CH₃)₂, HCO, H₂CO]	75		238
	$CH_3(CH=CH)CO_2C_2H_5$	87	C₆H₆, 0 hr., reflux	220

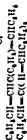|			
	C₆H₆ or C₆H₅CH₃, reflux C₂H₅OH, 2 days, 20 None, 10 hr, 170	25 45 60	37 34 35
	C₂H₅OH, 3-15 days, 20	93	34
	C₂H₅OH, 3-15 days, 20	91	34
	C₂H₅OH, 3-15 days, 20	89	34
	Dioxane, 7 hr, reflux; 12 hr, 20	30	221
	C₆H₆, reflux	70	239
	C₂H₅OH, 12 days, 20	7	34
	C₂H₅OH, 2 days, 20 C₆H₆, 6 hr, reflux	17 Quant.	3 220
	C₂H₅OH, 3-15 days, 20	71	34
	C₂H₅OH, 3-15 days, 20	89	34

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TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued
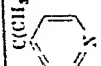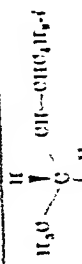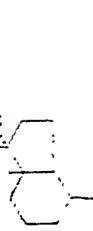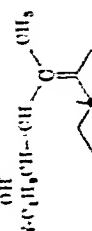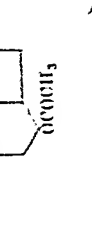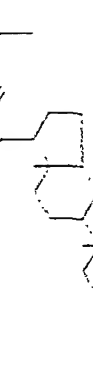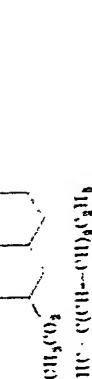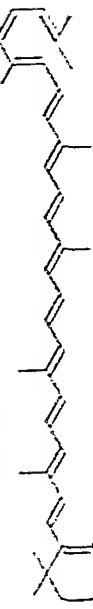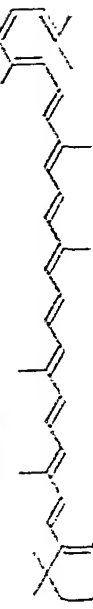
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_6 $(C_6H_5)_3P=CHCO_2C_2H_5$ (contd.)				
	(pyridyl)C(CH$_3$)=CHCO$_2$C$_2$H$_5$	90	C$_2$H$_5$OH, 3–15 days, 20	34
	CH$_3$CH=CH$_4$CO$_2$C$_2$H$_5$	82	C$_6$H$_6$, 0 hr, reflux	220
	(cyclohexyl)CH=CHCO$_2$C$_2$H$_5$	0	C$_2$H$_5$OH, 12 days, 20	34
	C$_6$H$_5$C(CH$_3$)=CHCO$_2$C$_2$H$_5$	58	None, 10 hr., 170	35
	CH$_3$·C(CH$_3$)C=CCH=C(CH$_3$)CH=CHCO$_2$C$_2$H$_5$	95		230
	C$_6$H$_5$CH=CHCH=CHCO$_2$C$_2$H$_5$	71	C$_6$H$_6$, 0 hr., reflux	220
	CH$_3$(CH=CH)$_2$CO$_2$C$_2$H$_5$	88	C$_6$H$_6$, 0 hr., reflux	220
	(CH$_3$)$_2$C=CH(CH$_3$)C(CH$_3$)=CHCH=CHCO$_2$C$_2$H$_5$	08	C$_6$H$_6$, 0 hr., reflux	217
	C$_2$H$_5$O$_2$CCH=C(CH$_3$)CH=CHCO$_2$C$_2$H$_5$	Quant.	C$_6$H$_6$, 0 hr., reflux	327
	CH$_3$(CO$_2$CH$_3$)CH=CHCO$_2$C$_2$H$_5$		C$_6$H$_6$, 0 hr., reflux	163
	C$_2$H$_5$O$_2$C(CH=CH)$_3$CO$_2$C$_2$H$_5$			
	(piperidyl, C$_6$H$_5$CH$_2$N)=CHCO$_2$C$_2$H$_5$	80	C$_2$H$_5$OH, 3–15 days, 20	34
	((C$_6$H$_5$)$_2$C=CHCO$_2$C$_2$H$_5$ CH$_3$)	54	None, 10 hr., 170	35
	(piperidyl CH$_3$, C$_6$H$_5$CH$_2$N) CHCO$_2$C$_2$H$_5$=CHCO$_2$C$_2$H$_5$	21	C$_2$H$_5$OH, 3–15 days, 20	34
	(cyclohexyl-N, CH$_3$)=CHCO$_2$C$_2$H$_5$ C$_6$H$_5$CH$_2$CH$_2$N	10	C$_2$H$_5$OH, 3–15 days, 20	34

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Structure		Conditions	Yield	Ref.
$C_2H_5CH_2CH_2N$—$CHCH_2C_2H_5$ with C_2H_5, $C_2H_5O_2C$		20	C_2H_5OH, 3–15 days, 20	34
$C_4H_5O_2C$	CH_3CH=$C(CH_3)CO_2CH_3$		CH_3I, 5 hr., reflux	39
	CH_2=$CHCH$=$C(CH_3)CO_2CH_3$		CH_3I, 12 hr., 20	164
		90	CH_3I, 3.5 hr., reflux	164
	CO_2CH_3	60	C_2H_5, 6 hr., reflux	39
			CH_3Cl_3, 5 hr., reflux	231
	CO_2CH_3		CH_3Cl_3, 5 hr., reflux	251
	CO_2CH_3		CH_3Cl_3, 6 hr., reflux	295–297
	CO_2CH_3		CH_3Cl_3, 6 hr., reflux	295–297
	CO_2CH_3		CH_3Cl_3, 6 hr., reflux	295–297
C_2H_5CH=$CCOCH_2C_2H_5$		41	None, 12 hr.	60

$(C_4H_9)_3P$=$C(CH_3)CO_2CH_3$

$(C_6H_5)_3P$=$CCOCH_2C_2H_5$

Note: References 291 to 404 are on p. 460.

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Reference
$(C_6H_5)_3P$—CHC_4H_9-t		60	Dioxane, 12 hr., 110	321
			Dioxane, 11 hr., 100	320
			$(C_2H_5)_2O$, 1 hr., 20; 15 hr., 65	378
$(C_6H_5)_3P$—CHCH—CHC$_3$H$_7$			$(C_2H_5)_2O$, 30 min., 80	200
$(C_6H_5)_3P$—CHCH—C(CH$_3$)$_3$			CH_2Cl_2, 20 hr., 20	205

Ylide	Product	Yield (%)	Conditions	References
(C₂H₅)₃P=CHCO₂C₂H₅	$(C_2H_5)_2C—CHCO_2C_nH_{2n}$	73	$(C_2H_5)_2O, -40; 4$ hr., 20	248
	$—CHCO_2C_6H_5$	40	$(C_2H_5)_2O, -30; 18$ hr., 20	248
	$—CHCO_2C_7H_{13}$	74, 46	$(C_2H_5)_2O, -30; 18$ hr., 20; $C_2H_5OH, 7$ hr., $-30; 18$ hr., 20	248, 248
$(C_2H_5)_3P=CHCH_2CH_2OC_2H_5$	$—CHCH_2CH_2OC_2H_5$	35, 39	$(C_2H_5)_2O, -30; 18$ hr., 20; $C_2H_5, -10; 15$ hr., 20	248, 248
$(C_2H_5)_3P=C(CH_3)CO_2C_2H_5$	$—C(CH_3)CO_2C_2H_5$	66	$(C_2H_5)_2O$	138
$C_6H_5C≡C$ ... $CO_2C_2H_5$		39	$CH_3CH_2, 6$ hr., reflux	39
	$p-CH_3C_6H_4CH=CHCH=CHCO_2C_2H_5$	33	$CH_3OH, 15$ min., 20	242
	$p-ClOC_6H_4CH=CHCH=CHCO_2C_2H_5$	25	$CH_2OH, 15$ min., 20	242
	$p-O_2NC_6H_4CH=CHCH=CHCO_2C_2H_5$	3		242
	$p-CH_3OC_6H_4CH=CHCH=CHCO_2C_2H_5$	40	$CH_3OH, 15$ min., 20	242
	$p-(CH_3)_2NC_6H_4CH=CHCH=CHCO_2C_2H_5$	48	$CH_3OH, 15$ min., 20	242
	$2,4,6-(CH_3)_3C_6H_2CH=CHCH=CHCO_2C_2H_5$	55	$CH_3OH, 15$ min., 20	242
	(structure with CH_3O, $CH=CHCH=CHCO_2C_2H_5$)	46	$CH_3OH, 15$ min., 20	242
	$2,3,4-(CH_3O)_3C_6H_2CH=CHCH=CHCO_2C_2H_5$	50	$CH_3OH, 15$ min., 20	242
	(structure with CH_3O_2C, CO_2CH_3)	35	$CH_3OH, 16$ min., 20	242
	(polyene structure, CH_3O_2C ... CO_2CH_3)	79	$C_4H_{11}, 6$ hr., reflux	232, 235
	(polyene structure)	79	$C_4H_{11}, 6$ hr. reflux	234

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Note References 231 to 404 are on p. 490.

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

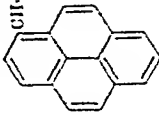### A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₅ (cont'd.)				
$(C_6H_5)_3P$–CHC(CH_3)·CHCN		80	CH_3CN, 1 hr., 20; 2.5 hr., 80	244
$(C_6H_5)_3P$–		95	$(C_2H_5)_2O$, 10 hr., 30	185
C₆				
$(C_4R_3)_3P$·CHCH·C_5H_{11}-n	$CH_3CO_2(CH_2)_2CH$–CHCH–CHC$_5$H$_{11}$-n	65	$(C_2H_5)_2O$, 0	327
$(C_6H_5)_3P$·CHCH·CHC$_3$H$_7$-n	$C_2H_5O_2C(CH_2)_6CH$–CHCH–CHC$_3$H$_7$-n	68	$(C_2H_5)_2O$, 2 hr., 0; 1 hr., 20	161
		75	Pet. ether, 3-12 hr., 0	320
	$CH_3CO_2(CH_2)_2CH$–CHCH–CHC$_3$H$_7$-n	70	Pet. ether, 2 hr., 0; 1 hr., 20	101,326
	$C_2H_5O_2C(CH_2)_2CH$–CHCH–CHC$_3$H$_7$-n	15	C_2H_5OH, 4 hr., reflux	325
	$(CH_3)_3C$–CHCH$_2$CH–C(CH$_3$)$_2$	12	$(C_2H_5)_2O$, 4 hr., 80-75	182
$(C_6H_5)_3P$·CHCH·CHC(CH_3)$_2$·CH$_2$	$(CH_3)_3C$·CH(CH$_2$)$_4$C(CH$_3$)–CH$_2$		$(C_2H_5)_2O$, 4 hr., 60-75	182
$(C_6H_5)_3P$·CHC·CC$_3$H$_7$-n	$C_3H_7O_2C(CH_2)_2CH$–CHC–CC$_3$H$_7$-n	47	C_2H_5OH, 1 day, reflux	325
$(C_6H_5)_3P$·CHCH·CH(CH$_2$)CH$_3$	$CH_3CO_2(CH_2)_2CH$–CH(CH)$_2$CH$_3$	70	$(C_2H_5)_2O$, 0	328
	$CH_3(CH$–CH)_2C$–C(CH$_2CH_3$)CH$_3$		$(C_2H_5)_2O/THF$, 30 min., 20	181
	$CH_3(CH$–CH)(C–O)_2CH(CH$_2$CH)CH$_3$		$(C_2H_5)_2O/THF$, 15 min., 20	181
	HC–CC(CH$_3$)–CHCH–CHCH–C(CH$_3$)C–CH		$(C_2H_5)_2O$, 2 hr., reflux	370,377
$(C_6H_5)_3P$–CHCH·C(CH$_3$)C·CH		10	C_6H_6, 0 hr., 00	280a
$(C_6H_5)_3P$·CHCH·CHCO$_2$C$_2$H$_5$	$C_2H_5O_2C(CH$–CH)_7CO_2C_2H_5$		C_6H_6, 5 hr., reflux; 12 hr., 20	103
$(C_6H_5)_3P$·CHCH·CHCH$_2$OCH$_3$			C_2H_5OH, 2 hr., 20	282
			C_6H_6, 2 hr., 20; 30 min., 00	55
			DMF, 2 hr., 20	55
		87	CH_3CN, 1 hr., 20; 3 hr., 85	244
		90	Tetramethylene sulfone, 1 hr., 20; 2 hr., 80	244

Reactant	Structure/Product	Yield (%)	Conditions	Refs.
$(C_6H_5)_3P$=CHCH=C(CH_3)CH=C(CH_3)CO_2CH_3, $C_6H_5(CH=CH)_3CH$=C(CH_3)CO_2CH_3		70	C_7H_8, 6 hr., reflux	232, 235
$(C_6H_5)_3P$=C(CH_3)CH=CHCO_2CH_3		84	C_7H_8, 6 hr., reflux	232, 235
	C=C		CH_2Cl_2, 6 hr., reflux	297
$(C_6H_5)_3P$=CH_2 CH_2CO_2CH_3, CO_2CH_3		76	C_2H_4, 6 hr., reflux	233, 234
$(C_6H_5)_3P$	C_6H_11CHCH	40	C_6H_6, 12 hr., reflux	40
	C_6H_11CH		$(C_2H_5)_2O$, 1 day, 20; 3 hr., reflux	113
C_7	CH_3CHCH_3C_6H_5	70	$(C_2H_5)_2O$, 12 hr., 20; 8 hr., 50	185
$(C_6H_5)_3P$=CHCH_3 $(C_6H_5)_3P$=CHCH=CH_2 $(C_6H_5)_3P$=CHCH=CHC_6H_5 $(C_6H_5)_3P$=CHCH=CHCO_2C_6H_5	CH(OC_2H_5)CH=CHCH(CH_3)CH=CH_2 H₂C(OC₂H₅)CH=CHCH(CH₃)CH=CH₂ HC=CHCH_2CHCO_2CH_3—CHCH_3	41 50	$(C_2H_5)_2O$, 10–12 hr., 20 H_2C(OCH_3)_2CH=CH_2, 2 hr., reflux $(C_4H_9)_2O$, 1 hr., 0	189, 189 160 258
	CH_3		$(C_2H_5)_2O$, 2 hr., 20 C_2H_4, 20 hr., 20 DMF, 16 hr., 20	287 287 287
$(C_6H_5)_3P$=CHC=CCCH_3)=CHCH_3	CH_3 C=C	209	THF, 16 hr., 20	209

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_7 (*cont.*)				
$(C_6H_5)_3P=CHCH=C(CH_3)CH(OC_2H_5)_2$	$CH(OC_2H_5)_2$	70	CH_3OH, 15 min., 55; 8 hr., 00	210
$(C_6H_5)_3P=CHCH_2CH_2CH_3$	$CH_2F·C(CH_3)=CHCH_2CH_2COCH_3$		DMF	218
$(C_6H_5)_3P=CHCH_2CH_2CO_2C_2H_5$	$n\text{-}C_{10}H_{13}CH=CH(CH_2)_3CO_2C_2H_5$	50	$(C_2H_5)_2O$, 3 hr., 05	114
$(C_6H_5)_3P=CH-$	$-CHCH=CH-$			159
	$-CH=CH-$	80	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 05	314
$(C_6H_5)_3P=CHC_6H_6$	$C_6H_5CH=CH_2$	04–75	$(C_2H_5)_2O$ DMF, 5 hr., 00	188, 180 113
	$C_6H_5CH=CHOC_2H_5$			
	C_6H_5CH-	00	$(C_2H_5)_2O$, 4 hr., 20; 1 day, 70	3
	$C_6H_5CH=CHC_6H_5$	82	$(C_2H_5)_2O$, 2 days, 20	2
		28	THF, 2 hr., reflux	00
		70	C_2H_5OH, 1 day, 20	3
	$p\text{-}ClCH_2C_6H_4CH=CHC_6H_5$		C_2H_5OH, 1 hr., 20	100
	$p\text{-}BrCH_2C_6H_4CH=CHC_6H_5$	70–75	C_2H_5OH, 1 hr., 20	100

$C_6H_5CH=CHCH=CHC_6H_5$		$(C_2H_5)_2O$, 3 hr., reflux	78	200
		THF, 12 hr., 20		200
		THF, 1 hr., 60		200
		C_2H_5OH, 30 min., 20	84	66
m-HOC$_6$H$_4$CH=CHCH=CHC$_6$H$_5$		C_2H_5OH, 3 days, 20	31	66
p-HOC$_6$H$_4$CH=CHCH=CHC$_6$H$_5$		C_2H_5OH, 3 days, 20	43	66
3-CH$_3$O-4-CH$_3$C$_6$H$_3$CH=CHCH=CHC$_6$H$_5$		$(C_2H_5)_2O$, 30 min., reflux	56	194
p-CH$_3$OC$_6$H$_4$CH=CHCH=CHC$_6$H$_5$		C_2H_5OH, 8 hr., 50	67	66
$(C_6H_5)_2C=CHC_6H_5$		$(C_2H_5)_2O$, 2 days, 75	46	3
		THF, 5 hr., reflux	23	90

	$(C_2H_5)_2O$, 1 hr., 20	75	3

p-O$_2$N·C$_6$H$_4$(C$_6$H$_5$)$_2$·CHC$_6$H$_5$		$(C_2H_5)_2O$, 10 hr., 75	47	3
m-C$_6$H$_5$CH=CHC$_6$H$_4$CH=CHC$_6$H$_5$		C_2H_5OH, 2 hr., 20	52	108

	C_2H_5OH, 1 day, 20	27	66

	DMF		201

C$_6$H$_5$CH=CHC$_6$H$_4$CH=CHC$_6$H$_5$		$(C_2H_5)_2O$/THF, 1 hr., 20		213
C$_6$H$_5$CH=CHC$_6$H$_4$CH=CHC$_6$H$_5$		$(C_2H_5)_2O$/THF, 1 hr., 20		213

	THF, 5 hr., 20		200

C$_6$H$_5$CH=CHC$_6$H$_4$CH=CHC$_6$H$_5$		$(C_2H_5)_2O$/THF, 1 hr., 20		213
C$_6$H$_5$CH=CHC$_6$H$_4$CH=CHC$_6$H$_5$		C_2H_5, 2 days, 20		113

$(C_6H_5)_2P=CHC_6H_5$-p

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TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₇ (contd.)				
$(C_6H_5)_3P=CHC_6H_3Cl_2-2,4$	(Cl, Cl substituted ring structure) $p-C_6H_4$(CH=CH—$C_6H_3Cl_2$)₂		DMF	201
$(C_6H_5)_3P=CHC_6H_4NO_2-m$ $(C_6H_5)_3P=CHC_6H_4NO_2-p$	$C_6H_5CH=CHCH=CHC_6H_4NO_2-m$ $p-CH_3OC_6H_4CH=CHC_6H_4NO_2-p$	95 80	C_2H_5OH, 20 C_6H_6, 4 hr., 20	210 100
	$m-C_6H_4$(CH=CH—NO_2)₂	51	C_2H_5OH, 2 hr., 40	00
$(C_6H_5)_3P=CHOC_6H_5$	—CHOC₆H₅ (cyclohexane)	98	$(C_2H_5)_2O$, 20	248
	$C_6H_5CH=CHOC_6H_5$ $(C_6H_5)_2C=CHOC_6H_5$	50 95	$(C_2H_5)_2O$, 20 $(C_2H_5)_2O$, 20	248 248
C₈ $(C_6H_5)_3P=CHCH_2CH_2O$ (tetrahydropyran ring)	$CH_3C($=$CH_2)_3CH=CHCH_2CH_2CH_2OH$		$(C_2H_5)_2O$, 3 hr., reflux	71
$(C_6H_5)_3P=CHC=C(CH_3)=CHCH_2OCH_3$	(cyclohexene ring)—C($=$C—CH₂OCH₃	10	$(C_2H_5)_2O$, 10 min., 20	200
$(C_6H_5)_3P=CHC($CH_3)$COC_9H_{17}-n$	$C_6H_5CH=C(CH_3)COC_9H_{17}-n$	40	C_6H_6, 1 day, reflux	32
$(C_6H_5)_3P=CHCH=C(CH_3)CH=CHCO_2CH_3$	CH_3O_2C—(long polyene chain)—CO_2CH_3		CH_2Cl_2; 1 hr., 20; 5 hr., reflux	230

CH₃Cl₃, 6 hr., reflux		297
CH₃Cl₃, 6 hr., reflux		297
THF, 2 hr., reflux		183, 184
(C₂H₅)₂O 1 day, 20		183, 184
(C₂H₅)₂O, 1 hr., 20, 3 hr., 65		158
THF, – 65; 18 hr., 20		69
C₂H₅OH, 3 hr., 20; 15 min., 70	23	
C₂H₅OH, 2 hr., 80	11	66
C₂H₅OH, 2 hr., 80		66
C₂H₅OH, 30 min., 20	75	105
C₂H₅OH, 30 min., 20	89	106
THF, 1 day, 20		113
C₇H₇, 4 hr., 20		106

$(C_6H_5)_3P=CHCH=$

$(C_6H_5)_3P=CHCH=CH-C_6H_4-CH_3$

$(C_6H_5)_3P=CHCH_2CH_2CH_2P^a$

$(C_2H_5)_3P=CHCH_2CH_2OCH_3^a$

Note: References 391 to 401 are on p. 490.

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. *Mono-ylides as Starting Materials—Continued*

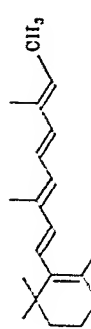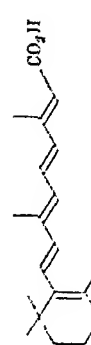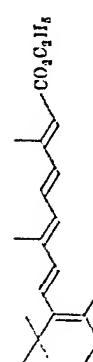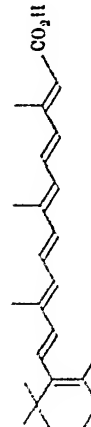| Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₆ (*cont.*)				
(C₆H₅)₃P=CHC₆H₅(O₂CH₂)-3,4	*p*-C₆H₄ $\left(\text{CH=CH} \left\langle \substack{O \\ O} \right\rangle \text{CH}_2 \right)_2$		DMF	201
(C₆H₅)₃P=CHOC₆H₄CH₃-*p*	(C₂H₅)₂C=CHOC₆H₄CH₃-*p*	72	(C₂H₅)₂O, 20	248
	=CHOC₆H₄CH₃-*p* (cyclohexane)	82	(C₂H₅)₂O, 20	248
		58	*t*-C₄H₉OH, 8 hr., 65	248
	C₆H₅CH=CHOC₆H₄CH₃-*p*	75	(C₂H₅)₂O, 20	248
		64	*t*-C₄H₉OH, 8 hr., 65	248
	(C₆H₅)₂C=CHOC₆H₄CH₃-*p*	67	(C₂H₅)₂O, 20	248
		61	*t*-C₄H₉OH, 8 hr., 65	248
	CH=CHCH(CH₃)=CHOC₆H₄CH₃-*p*	73	(C₂H₅)₂O, 2 hr., 20	248
	CH=CHCH(CH₃)=CHOC₆H₄CH₃-*p*	75	(C₂H₅)₂O, 2 hr., 20	248
	o-C₆H₄ $\left(\text{CH=CHO} \left\langle \right\rangle \text{CH}_3 \right)_2$	62	(C₂H₅)₂O, 20	248
(C₆H₅)₃P=CHCOC₆H₅	C₆H₅CH=CHCOC₆H₅	70	C₆H₆, 3 days, reflux	32
(C₆H₅)₃P=CClCOC₆H₅	C₆H₅CH=CClCOC₆H₅	Quant.	THF, 30 hr., reflux	31
	p-O₂NC₆H₄CH=CClCOC₆H₅	64	None, 2 days, 100	60
(C₆H₅)₃P=CBrCOC₆H₅	*p*-O₂NC₆H₄CH=CBrCOC₆H₅	60	C₆H₆, 35 hr., reflux	59
			C₆H₆, 35 hr., reflux	59

C_7 (C₆H₅)₃P=CHCH=CHC₃H₇-n	H(C=CH)₃CH₂C₃H₇-n	(C₃H₇)₂O, 2 hr, 20	257
(C₆H₅)₃P=CHCH=CHCHCO₂C₂H₅	H(C=CH)₂(CH₃)₂CH=CH₂	(C₂H₅)₂O, 2 hr, 20	160
(C₂H₅)₃P=CHCH₂CH₂CO₂C₂H₅	CH₃CH=C(CH₃)CH₂CO₂C₂H₅	DMF	114
(C₆H₅)₃P=CHCH=CHCOCH₃	CH₂OOCCH₃	DMF, 5 hr, 20	290
(C₆H₅)₃P=CHCH₃ ⊖ CH₂O ⊖	CH₂OH —CHCH₃	THF, −25; 12 hr, 20	69
(C₆H₅)₃P=CHCH=CHCH₂C₆H₅	p-CH₃CH₂CH₂CH=CHCH=CHCH₃	C₂H₅OH, 20	63
	p-CH₃OCH₂CH=CHCH=CHCH₃	C₂H₅OH, 20	76
	p-CH₃CONHC₆H₄CH=CHCH=CHC₆H₅	C₂H₅OH, 20	61
	(C₆H₅)₂C=CHCH=CHCH=CHC₆H₅	C₂H₅OH, 20	61
	C₆H₅CH=CH(C₆H₄)₂CH=CHCH=CHC₆H₅	(C₂H₅)₂O, 12 hr, 20	64
		(C₂H₅)₂O, 12 hr, 50	61
		(C₂H₅)₂O/THF, 1 hr, 20	213
	C₆H₅CH=CHCH=CH-C₆H₅	C₂H₅OH, 2 hr, 20	211
	m-C₆H₄(CH₂CH=CHCH=CHC₆H₅)₂	C₂H₅OH, 2 hr, 20	211
	p-C₆H₄(CH=CHCH=CHC₆H₅)₂	C₂H₅OH, 4 hr, 70	59
		C₂H₅OH, 20 min., 80	57

Note: References 391 to 404 are on p. 490.

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₉ (contd.) $(C_6H_5)_3P—CHCH—CHC_6H_5$	(pyrene)CH—CHCH—CHC₆H₅	62	C_2H_5OH, 2 hr., 20	211
	$C_6H_5(CH—CH)_2C(C_6H_5)—CHCH—CHC_6H_5$		THF, 15 min., 20; 45 min., reflux $(C_2H_5)_2O/THF$, 1 hr., 20	213
	$(C_6H_5CH—CH)_2C—CHCH—CHC_6H_5$		$(C_2H_5)_2O/THF$, 1 hr., 20	213
	$C_6H_5(CH—CH)_2C—CHCH—CHC_6H_5$ $\quad CH—CHC_6H_5$		$(C_2H_5)_2O/THF$, 1 hr., 20	213
	$(C_6H_5CH—CHCH—CH)_2C—CHCH—CHC_6H_5$		$(C_2H_5)_2O/THF$, 1 hr., 20	213
$(C_6H_5)_3P—CHC_6H_3(OCH_3)_2$-2,4	$p\text{-}C_6H_4\left(CH—CH\begin{smallmatrix}—OCH_3\\ \\OCH_3\end{smallmatrix}\right)_2$		DMF	201
$(C_6H_5)_3P—CHCH_3COC_6H_5$	$C_6H_5—C_6H_5$ (cyclohexadiene)	12	C_6H_6, 30 hr., reflux	203
$(C_6H_5)_3P—CHCH_3CO_2CH_3$-p	$C_6H_5CH—CHCH—CHC_6H_4CO_2CH_3$-p	38	C_2H_5OH, 20	210
$(C_6H_5)_3P—CHCH_3CO_2CH_3$-p	$p\text{-}C_6H_4\left(CH—CH\begin{smallmatrix}\\CO_2CH_3\end{smallmatrix}\right)_2$	73	C_2H_5OH, 30 min., 20 DMF or $(CH_3)_2SO$	103, 100, 200
$(C_6H_5)_3P—CHC_6H_4N(CH_3)_2$-p	$C_6H_5CH—CHCH—CHC_6H_4N(CH_3)_2$-p	60	C_2H_5OH, 20	210
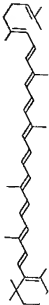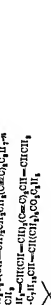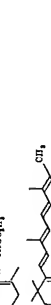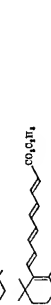
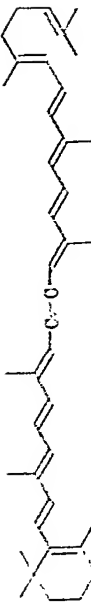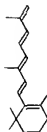|			
C_{10} (C_5H_9)$_3$P=CH$_2$		CH$_2$Cl$_2$, 5 hr., reflux	278, 277
(C_5H_9)$_3$P=CH$_2$		(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	51	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	72	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	63	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	68	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	61	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397
	46	(C$_2$H$_5$)$_2$O, 3–4 hr, reflux	397
	60	(C$_2$H$_5$)$_2$O, 3–4 hr., reflux	397

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION
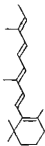
A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_{10} $((C_4H_9)_3t-CH-$ (contd.)	$C(CH_3)-CH$	53	$(C_2H_5)_2O$, 3–4 hr., reflux	307
	p-ClC$_6$H$_4$CH–CH	62	$(C_2H_5)_2O$, 3–4 hr., reflux	307
	CH=CH, H$_3$CO, O	50	$(C_2H_5)_2O$, 3–4 hr., reflux	307
	$(CH_3)_2C-CH(CH_2)_2C(CH_3)-CH$	43	$(C_2H_5)_2O$, 3–4 hr., reflux	307
	p-(CH$_3$)$_2$CHC$_6$H$_4$CH–CH	75	$(C_2H_5)_2O$, 3–4 hr., reflux	307
	CH$_3$CO$_2$(CH$_2$)$_9$CH–CH	53	$(C_2H_5)_2O$, 5 hr., 0; 0–7 hr., 20	328
		70	CH$_2$Cl$_2$, 15 min, 30; 5 hr., reflux DMF, 2 hr., 20	275, 276, 274

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Structure	Yield	Conditions	Ref.
(structure)		CH_2Cl_2, 10 min, 30; 5 hr, reflux, DMF, 2 hr, 20	275, 276, 274
(structure)		CH_2Cl_2, 5 hr, reflux	284
(structure)	70	CH_3OH	279
(structure)	55	CH_3OH	279
(structure)	47	$(C_2H_5)_2O$, 2 hr, reflux	241
	1	$(C_2H_5)_2O$, 2 days 0	259
	50	DMF	114
(structure)		DMF, 5 hr, 60	113
(structure)	60	$(C_2H_5)_2O$, 2 hr, reflux; DMF, 8 hr, 20	293, 293
(structure)	65	$DMF/(C_2H_5)_2O$, 2 hr, 20	293

$(C_6H_5)_3P=CH_2$

$(C_6H_5)_3P=CH_2$

$(C_6H_5)_3P=CHCH=CH_2C(=O)_2C_2H_5; = CH_2CH_2C(CH=CH_2)CH=CHCH_3$
$(C_6H_5)_3N=CHCH=CHC(CH_3)=CH_2; CH=CHCH_2CH_2COCO_2C_2H_5$
$(C_6H_5)_3N=CH-CH=CH-CH=CHCH_3$

$CH_2=CHCH=CH_2C(=O)=O_2CH_2; CH_2CH_2CH=CHCH_3$
$n-C_3H_7CH=CHCH(CH_2)_4CO_2C_2H_5$

$(C_6H_5)_3N=CH$

$(C_6H_5)_3N=CH$
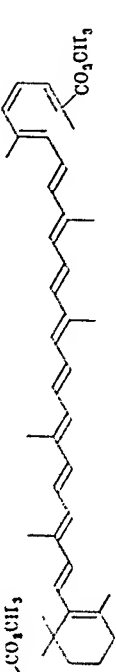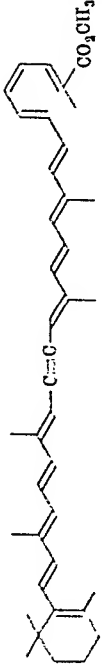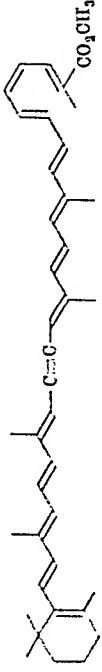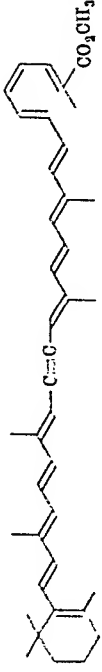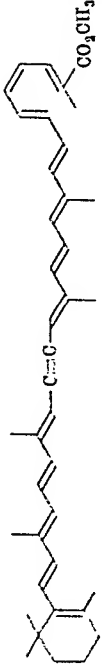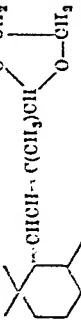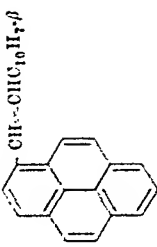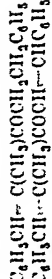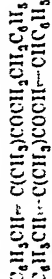
Note: References 291 to 404 are on p. 400.

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. *Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₁₅ $(C_6H_5)_3P=CH—$ (contd.)	$CH=CH(CH_2)_3CO_2CH_3$	53	$(C_2H_5)_2O$, 3 hr., 0; 6 hr., 20; 1 hr., reflux	328
	$CH=CH(CH_2)_3CH_2OCOCH_3$	68	$(C_2H_5)_2O$, 0	328
	(polyene structure)		THF, 1 hr., 60	200
	(polyene structure, $C=C$)		THF, 1 hr., 60	209
	(polyene structure)	3	CH_2Cl_2, 15 min., 30; 5 hr., reflux; DMF, 1 hr., 20	273 274
	(polyene structure, $C=C$)	3	C_6H_6, 6 hr., 60 $(C_2H_5)_2O/C_6H_6$, 1 hr., 40	273 275
$(C_6H_5)_3P=C(CH_2C_6H_5)CO_2CH_3$	$C_6H_5CH=C(CH_2C_6H_5)CO_2CH_3$	42	C_6H_6, 10 hr., reflux	40

C₁₁ | structures | conditions | yields | refs

C_{11} $(C_6H_5)_3P$=CHCH=CH$_2$$^{n-m}$ n-C$_7$H$_{15}$CH=CH$_2$C≡Cn $(C_6H_5)_3P$=CHCH$_2$CH=CO$_2$C$_2$H$_5$$^{n-m}$ i-C$_3$H$_7$C≡Cn(C≡C)$_2$(CH$_3$)$_2$CO$_2$C$_2$H$_5$$^{n-l}$		$(C_6H_5)_2O/THF$, 20 min., 20 $(C_6H_5)_2O$, 30 min., 20 $(C_6H_5)_2O$, 30 min., 20	181 180 180
$(C_6H_5)_3P$=CH— [structure OCH₃]	[structure OCH₃]	19	278
$(C_6H_5)_3P$=CH— [structure OCH₃]	[structure OCH₃]	CH₃OH	278
$(C_6H_5)_3P$=CH— [structure OCH₃]	[structure OCH₃] CH₃OH	278
	n-C$_7$H$_{15}$CH=CH(CH$_2$)$_2$CO$_2$C$_2$H$_5$	64 DMF, 20	278
	n-C$_7$H$_{15}$(CH$_2$)$_3$=CH=CH(CH$_2$)$_3$CO$_2$C$_2$H$_5$ n-C$_6$H$_{13}$(CH$_2$)$_3$CH(CH$_2$)$_3$CO$_2$C$_2$H$_5$ n-C$_6$H$_{13}$(CH$_2$)$_3$CO$_2$C$_2$H$_5$ n-C$_6$H$_{13}$(CH$_2$)$_4$CO$_2$C$_2$H$_5$ n-C$_6$H$_{13}$CH=CH(CH$_2$)$_3$CO$_2$C$_2$H$_5$	73 DMF, 20 25 DMF 22 DMF 50 DMF 44 DMF, 20	114,170,171,172 114 171 171 114 114 170,171,172 114
$(C_6H_5)_3P$=CH— [structure CO₂CH₃]	[structure C=O CO₂CH₃]	CH₂Cl₂, 5 hr., reflux	208
$(C_6H_5)_3P$=CH [structure]	[structure C=O CO₂CH₃]	CH₂Cl₂, 6 hr., reflux	207

Note: References 391 to 404 are on p. 490.

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-olefins as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_{11} $(C_6H_5)_3P=CH$—(*cont'd.*)	[structure with CO_2CH_3]		CH_2Cl_2, 0 hr., reflux	207
	[structure with CO_2CH_3]		CH_2Cl_2, 0 hr., reflux	207
$(C_6H_5)_3P=CHCH$—	[structure]		$(C_2H_5)_2O/C_6H_6$, 20 min., 20; 0 hr., 00	214
$(C_6H_5)_3P=CHC_{10}H_7$-β	$C_6H_5CH=CHC_{10}H_7$-β β-$C_{10}H_7CH=CHC_{10}H_7$-β	20 38	C_2H_5OH, 23 hr., 20 C_2H_5OH, 23 hr., 20	107 107
	$CH=CHC_{10}H_7$-β [pyrene structure]	61	C_2H_5OH, 23 hr., 20	107
$(C_6H_5)_3P=CH(CH_2)_5OC_6H_5$	[cyclopentene structure] C_6H_5	24	C_2H_5OH, 30 min., reflux	202
$(C_6H_5)_3P=C(CH_3)COCH_2CH_2C_6H_5$ $(C_6H_5)_3P=C(CH_3)COCH=CHC_6H_5$	$C_6H_5CH=C(CH_3)COCH_2CH_2C_6H_5$ $C_6H_5CH=C(CH_3)COCH=CHC_6H_5$	64 81	C_6H_6, 3 days, reflux C_6H_6, 4 days, reflux	32 32

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C₁₅	(C₂H₅)₃P=CH—CH=CH₂	HₙC≡CH—CH=CH,Hₙ=n	(C₂H₅)₂O	159
		C₂H₅OCH=CH(CH₂)₃,n=n	THF/(C₂H₅)₂O, 1 day, 20	115
	(C₂H₅)₃P=CH		CH₃C₆H₅, 90 hr, 20; 20; 61 hr, reflux	226
	C₂H₅O₂C			
	(C₂H₅)₃P=CH—CH₂CH=CH—CH₂R		C₂H₅, 90 hr, reflux	40
	CO₂C₂H₅			
	(C₂H₅)₃P=CHCH₂		60	(C₂H₅)₂O, 1 hr, 20	72
		CH₂CH—CH=CH=CH₂C₄(CH₃)₂CH₂,CH₂,CH₂,CH(OH)CH₂CH₂OH		
		C₅H₁₁		
	(C₂H₅)₃P=CH	CH=CHCH₃	(C₂H₅)₂O, 1 hr, 20; 3 hr, 65	70
C₁₆	(C₂H₅)₃P=CHCH₃	(CH₃)₂O=CHCH(CH₃)₂CO₂C₂H₅	55	DMF, 20	114
		C₂H₅CH₂CH=CH(CH₃)₂CO₂C₂H₅	47	DMF, 20	114
		n-C₃H₇CH₂—CH=CH(CH₃)₂CO₂C₂H₅	52	DMF, 20	114
		n-C₄H₉(CH₃)₂—CH(CH₃)₂CO₂C₂H₅	47	DMF, 20	170, 170, 170, 171
		n-C₅H₁₁CH₂—CH=CH(CH₃)₂CO₂C₂H₅	71	DMF, 20	114, 170, 171
		n-C₆H₁₃CH₂—CH=CH(CH₃)₂CO₂C₂H₅	67	DMF, 20	114, 171
		n-C₇H₁₅CH₂—CH=CH(CH₃)₂CO₂C₂H₅	54	DMF, 20	114, 171
	(C₂H₅)₃P=C(CH₃)₂CH=CH		THF, 3 hr, 20	210
		CH₂OH		
	(C₂H₅)₃P=C(CH₃)₂CH=CH		DMF, 1 day, 20	113, 140
		OC₃H₇		

Note. References 391 to 404 are on p. 490.

TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. *Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_{15} $(C_6H_5)_3P=C(CH_3)CH=CH-$ (cont.)			$(C_2H_5)_2O$, 2 hr., 20; 6 hr., reflux	240
			DMF, 2 hr., 20	240
		70	C_6H_6, 1 hr., 20 DMF, 2 hr., 20	240 289
		80	DMF, 30 min., 20 DMF, —40; 5 min., —10	291 292
		70	DMF, 2 hr., 20 DMF, 1 hr., 70 DMF, —40; 5 min., —10	289 289 292
			DMF, 15 min., 20	240

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209	THF, 2 hrs., 60		
240, 272	DMF, 1 hr., 20		
49	CHCl₃, 3 hr., reflux	84	
49	CHCl₃, 3 hr., reflux	95	
49	CHCl₃, 3 hr., reflux	37	

C_6H_5CH

$p\text{-}O_2NC_6H_4CH$

$p\text{-}CH_3OC_6H_4CH$

$(C_2H_5)_2P$

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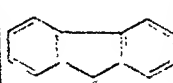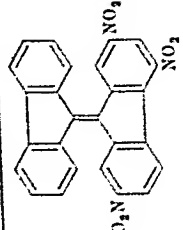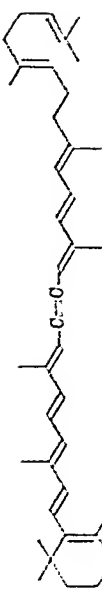
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

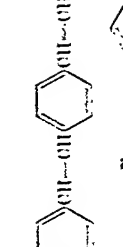| Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₁₀ (C₆H₅)₃P=C(contd.)		Quant.	CHCl₃, 3 hr., reflux	49
C₁₄ (C₆H₅)₃P=C(C₃H₅)	C₄H₅CH=C(C₃H₅-n)COCH₂CH₂C₆H₅ (C₆H₅)₂C=C~C(C₆H₅)₂	90 40	C₆H₆, 3 days, reflux THF, 12 hr., reflux	32 123
C₁₅ (C₆H₅)₃P=C~C(C₆H₅)₂			DMF, 12 hr., 0	205
C₁₅ (C₆H₅)₃P=CHCH~C(CH₃)CH₂CH₂			DMF, 10 hr., 20	204

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$(C_6H_5)_3P=CHCH=C(CH_3)CH=CH-$

	Conditions	
OC₂H₅	DMF, 12 hr, 20	269, 270
	DMF, 3 hr, 20	269, 270
	DMF, 8 hr, 20; DMF, 2 hr, 20; C₂H₅OH, 1 hr, −15; 12 hr, 20	297, 270, 294, 295
CO₂H	DMF, 4 hr, 0; CH₃OH, 1 hr, 20; C₂H₅OH, 1 hr, −15; 12 hr, 20	284, 270, 296, 295
OC₂H₅	20	269, 270
CO₂CH₃	CH₃OH·C₆H₆, 5 hr, 20; CH₃OH, 10 hr, 20	285, 286
CH₂OCOCH₃	None, 3 hr, 8; CH₃OH, −20; 5 hr, 0	
	DMF, 3 hr, 0; CH₃OH, 2 hr, 0; −10; 12 hr, 20	270, 294, 295

Note. References 301 to 404 are on p. 490.

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TABLE VI—*Continued*

OLEFINS PREPARED BY THE WITTIG REACTION

A. *Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_{15} $(C_6H_5)_3P=CHCH=C(CH_3)CH=CH$ (contd.)		70	$(C_2H_5)_2O$ THF, 30 min., −30; 18 hr., 20 C_6H_6 DMF, 30 min., −10; 2 hr., 20 DMF, 0 hr., 20 CH_3OH, 1 hr., 20 CH_3OH, 45 min., −30; 4 hr., 20 C_2H_5OH, 30 min., −10; 2 hr., 20	283 285 283 284 283 284 285 285
	($CO_2C_2H_5$ product)		DMF, 10 hr., 20	270
	($CO_2C_4H_9$ product)		DMF, 15 min., 20 CH_3OH, 15 min., 20 C_2H_5OH, 1 hr., 20	269, 294 270 294
	(CO_2H product)		$(C_2H_5)_2O$ or C_6H_6, 10 hr., 20 DMF, 1–3 hr., 20	54 208– 270
			C_2H_5OH/DMF, 3 hr., 20	208
	($C{\equiv}C$ product)		DMF, 1–2 hr., 20 DMF, 20 hr., 20 C_2H_5OH, 2 hr., 20; 10 min., reflux	268, 270 204 54

Structure	Conditions	Yield	Reference
(long conjugated polyene with two ring systems)	DMF, 16 hr., 20		264
$(C_3H_7)_3P=CHCH=C(CH_3)CH=CH-$ (polyene with ring)	C_2H_5OH, 10 mℓ₀, −10; 2 hr., 20		289
$(C_5H_6)_3P=CHCH=CHCH=C(C_2H_5)_3$ (polyene with rings)	C_2H_5OH, 2 hr., 20	72	211
$(C_2H_5)_3P=CHCH=CHCH=C(C_2H_5)_3$ (anthracene, $CO_2C_2H_5$)	C_2H_5OH, 2 hr., 20	62	211
$(C_2H_5)_3P=CH$ ... $CH=CHC_6H_4$ (anthracene) $CH-CHClC_6H_4$	C_2H_5OH, 2 hr., 20	57	211
$p-C_6H_4(CH_2-4[CH=CH-C(C_2H_5)_3]_2$ $CH=CHCH=C(C_2H_5)_3$	C_2H_5OH, 2 hr., 20		211
$[CH=CH-\langle\rangle-]_n$	C_2H_5OH, 20	72–73	167
$[CH=CH-\langle N \rangle-]_n$ (pyridinium)	C_2H_5OH, 2 hr., 20	54	109
$[CH=CH-\langle N \rangle-]_n$ (pyridinium)	C_2H_5OH, 2 hr., 20		109

Note. References 391 to 404 are on p. 490

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TABLE VI—Continued

Olefins Prepared by the Wittig Reaction

A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_{13} $(C_6H_5)_3P=CH\cdot CH=CHC_6H_5$ (cont'd.)		45	C_2H_5OH, 2 hr., 20	108
	$p\text{-}BrCH_2C_6H_4CH=CHC_6H_5$	63–65	C_2H_5OH, 1 hr., 20	100
			C_2H_5OH, 2 hr., 20	105
		38–40	C_2H_5OH, 2 hr., 20	211
C_{16} $(C_6H_5)_3P=CH\cdot CH=CHC_6H_4CH_3\text{-}p$		57	C_2H_5OH	100
C_{17} $(C_6H_5)_3P=CH-$		91	C_2H_5OH	107
C_{18} $(C_6H_5)_3P=CHCO_2C_{16}H_{33}\text{-}n$			H_2Cl_2, 5 hr., reflux	30

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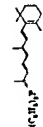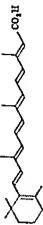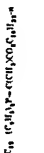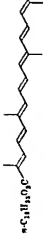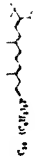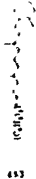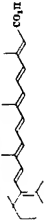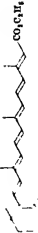
$(C_6H_5)_3P$	CO_2H	DMF, 1 hr, 20	270
C_{60} $(C_6H_5)_3P=C(CH_3)CO_2C_{18}H_{37}$	$CO_2C_{18}H_{37}$	CH_2Cl_2, 5 hr, reflux	39
C_{60} $(C_6H_5)_3P$		$(C_2H_5)_2O$, 3 hr, 20	267
$(C_6H_5)_3P$	CO_2H	DMF, 15 min, 20	266
	$CO_2C_2H_5$	DMF, 3 hr, 0; 1 hr, 20	266
		CH_3OH, 15 hr, 20	266
	$CO_2C_2H_5$	C_2H_5OH, 2 hr, 20	266

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

A. Mono-ylides as Starting Materials—Continued

Product (Ylide)	Yield, %	Solvent, Time, Temperature, °C.	References
C_5 $(C_6H_5)_3P=CH-\left[\text{—}C_6H_4-CH=CH\text{—}\right]_3 H$			
$\left[\text{—}C_6H_3(N)-CH=CH\text{—}\right]_3 H$	50	C_2H_5OH, 2 hr., 20	108
$\left[\text{—}C_6H_3(N)-CH=CH\text{—}\right]_3 H$		C_2H_5OH, 2 hr., 20	108
$\left[\text{—}C_6H_3(CH_3)-CH=CH\text{—}\right]_4 H$		C_2H_5OH, 2 hr., 40	100
$\left[\text{—}C_6H_4-CH=CH\text{—}\right]_6 H$	42	C_2H_5OH, 2 hr., 40	100
$\left[\text{—}C_6H_4-CH=CH\text{—}\right]_7 H$	32	C_2H_5OH, 2 hr., 40	100

B. Bis-ylides as Starting Materials

Product (Ylide)	Yield, %	Solvent, Time, Temperature, °C.	References
C_4 $[(C_6H_5)_3P=CHCH=P(C_6H_5)_3]$		CH_5OH	100

		%	Conditions	Ref.
C_5	$(C_6H_5)_3P=CHCH_2CH=N-C_5H_{11}$			

Structure	Reagent/Conditions	Yield	Conditions	Ref.
	$C_5H_{11}CH=CHCH_2CH=CHC_5H_{11}$	28	$(C_2H_5)_2O/THF, 6 hr., reflux$	52
		65	$(C_2H_5)_2O, 10 hr., 65$	52
	$(C_6H_5)_3P=CHCH_2CH=N-C_5H_{11}$, $C_5H_{11}OCH=CHCH_2CH=CHOC_5H_{11}$		THF, 2 days, 20	113
		18	$(C_2H_5)_2O/THF, 20 hr., 70$	52
	$C_5H_{11}CH=CHCH_2CH=CHC_5H_{11}$	75	$C_5H_{11}OH, 8 days, 20$	74
		0	$(C_2H_5)_2O, 2 hr., 20; 3 hr., 60$	74
		13	THF, 1 hr., reflux	300
			THF	301
		35	$C_5H_{11}OH, 5 days, 20$	74
	$(C_6H_5)_3P=CHCH_2CH=C(CH_3)_2$	26	$i-C_4H_9OH, 5 hr., 25$	302
		50	$(C_2H_5)_2O, 36 hr., 20, 3 hr., 60$	74
		17	$(C_2H_5)_2O, 14 hr., 65$	185
	$(C_6H_5)_3P=CHCH=CHCH=N-C_5H_{11}$, $C_5H_{11}CH=CHCH_2CH_2$	15	$(C_2H_5)_2O/THF, 1 hr., reflux$	52
				212
			$C_5H_{11}OH$	212
			$C_5H_{11}OH$	212
			THF, 4 hr., reflux	209
			$C_5H_{11}OH$	212
			$C_5H_{11}OH$	212

TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

B. Bis-ylides as Starting Materials—Continued

	Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₃	$(C_6H_5)_3P \cdot CH(CH_2)_3CH=P(C_4H_3)_3$	$CH_2=CH(CH_2)_3CH=CH_2$	45	$(C_2H_5)_2O$	180, 188
C₈	$(C_6H_5)_3P=CH$ (o-xylylidene)	$o\text{-}C_6H_4(CH=CHC_6H_5)_2$	84	C_2H_5OH, 30 min, 20; 2 hr, reflux	201a
		$o\text{-}C_6H_4(CH=CHC_6H_4CH_3\text{-}o)_2$	53	C_2H_5OH, 30 min, 20; 4 hr, reflux	201a
C₉	$(C_6H_5)_3P=CH$ (p-xylylidene) $CH=P(C_6H_5)_3$	$p\text{-}C_6H_4(CH=CH_2)_2$	42	$(C_2H_5)_2O$	188, 189
		$p\text{-}C_6H_4\left(CH=CH\text{—}\overset{\displaystyle N}{\bigcirc}\right)_2$	56	C_2H_5OH, 2 hr, 20	108
		$p\text{-}C_6H_4(CH=CHC_6H_5)_2$	32	C_2H_5OH, 1 hr, 80	60
			86	C_2H_5OH, 2 hr, 20	193
		$p\text{-}C_6H_4(CH=CHC_6H_4Cl\text{-}p)_2$	13	C_2H_5OH, 1 day, 20	103
		$p\text{-}C_6H_4(CH=CHC_6H_4NO_2\text{-}m)_2$	83	C_2H_5OH, 1 day, 20	103
		$p\text{-}C_6H_4(CH=CHC_6H_4NO_2\text{-}p)_2$	60	C_2H_5OH, 1 day, 20	103
		$p\text{-}C_6H_4(CH=CHC_6H_4CH_3\text{-}p)_2$	81	C_2H_5OH, 12 hr, 20	103
		$p\text{-}C_6H_4(CH=CHC_6H_4OCH_3\text{-}p)_2$	91	C_2H_5OH, 12 hr, 20	103
		$p\text{-}C_6H_4(CH=CHCH=CHC_6H_5)_2$	88	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4(CH=CHCH=CHC_6H_4NO_2\text{-}m)_2$	70	C_2H_5OH, 12 hr, 80	60
		$p\text{-}C_6H_4(CH=CHC_6H_4NH(COCH_3\text{-}p)_2$	05	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4[CH=CHC(CH_3)=CHC_6H_5]_2$	72	C_2H_5OH, 12 hr, 20	193
		$p\text{-}C_6H_4(CH=CHCH=CHC_6H_4CH_3\text{-}p)_2$	83	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4(CH=CHCH=CHC_6H_4OCH_3\text{-}p)_2$	Quant.	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4[CH=CHCH=CHC_6H_4CH_3\text{-}p]_2$	13	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4[CH=CHCH=CHC_6H_4N(CH_3)_2\text{-}p]_2$	Quant.	C_2H_5OH, 12 hr, 20	210
		$p\text{-}C_6H_4\left(CH=CH\text{—}\bigcirc\text{—}CH=CH\text{—}\overset{\displaystyle N}{\bigcirc}\right)_2$	35	C_2H_5OH, 2 hr, 20	108

$p\text{-}C_6H_4\left(CH=CHCH=CHC_6H_5\right)_2$	C_2H_5OH, 2 hr., 40	100
$p\text{-}C_6H_4\left(CH=CH\right)_2C_6H_5$	C_2H_5OH, 2 hr., 40	105
$p\text{-}C_6H_4\left(CH=CHCH=CHCH=CH\right)_2C_6H_5$	75–78	C_2H_5OH	100
$OHC\text{-}C_6H_4\left[CH=CH\text{-}CH=CH\text{-}C_6H_4\right]_2CHO$	Quant., C_2H_5OH	208

C_{10} $(C_6H_5)_3P$

$P(C_6H_5)_3$	91	$(C_3H_7)_2O$, 8 hr., reflux	80, 271
$(C_6H_5)_3P$	39	$(C_3H_7)_2O$, 8 hr., reflux	80, 271
$P(C_6H_5)_3$	65	$(C_3H_7)_2O$, 8 hr., reflux	80, 271
	42	$(C_3H_7)_2O$, 8 hr., reflux	80, 271

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TABLE VI—Continued

Olefins Prepared by the Wittig Reaction

B. Bis-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_6 $(C_6H_5)_3P$—$CH(CH_2)_4CH$—$P(C_6H_5)_3$	CH_2—$CH(CH_2)_3CH$—CH_2	45	$(C_2H_5)_2O$	180, 188
	o-$C_6H_4(CH$—$CHC_6H_5)_2$	84	C_2H_5OH, 30 min., 20; 2 hr., reflux	201a
$(C_6H_5)_3P$—CH	o-$C_6H_4(CH$—$CHC_6H_4CH_3$-$o)_2$	53	C_2H_5OH, 30 min., 20; 4 hr., reflux	201a
C_2 $(C_6H_5)_3P$—CH	m-$C_6H_4(CH$—$CH_2)_2$	42	$(C_2H_5)_2O$	188, 180
CH—$P(C_6H_5)_3$	p-$C_6H_4\left(CH$—CH—\underset{N}{\bigcirc}\right)_2$	50	C_2H_5OH, 2 hr., 20	108
	p-$C_6H_4(CH$—$CHC_6H_5)_2$			
	p-$C_6H_4(CH$—CHC_6H_4Cl-$p)_2$	32	C_2H_5OH, 1 hr., 80	68
	p-$C_6H_4(CH$—$CHC_6H_4NO_2$-$m)_2$	86	C_2H_5OH, 2 hr., 20	103
	p-$C_6H_4(CH$—$CHC_6H_4NO_2$-$p)_2$	13	C_2H_5OH, 1 day, 20	103
	p-$C_6H_4(CH$—$CHC_6H_4CH_3$-$p)_2$	83	C_2H_5OH, 1 day, 20	103
	p-$C_6H_4(CH$—$CHC_6H_4OCH_3$-$p)_2$	60	C_2H_5OH, 1 day, 20	103
	p-$C_6H_4(CH$—$CHC_6H_5)_2$	91	C_2H_5OH, 12 hr., 20	103
		61	C_2H_5OH, 12 hr., 20	103
		98	C_2H_5OH, 12 hr., 20	210
		70	C_2H_5OH, 12 hr., 80	68
	p-$C_6H_4(CH$—$CHCH$—$CHC_6H_4NO_2$-$m)_2$	65	C_2H_5OH, 12 hr., 20	210
	p-$C_6H_4(CH$—$CHC_6H_4NHCOCH_3$-$p)_2$	72	C_2H_5OH, 12 hr., 20	103
	p-$C_6H_4(CH$—$CHC(CN)$—$CHC_6H_5)_2$	83	C_2H_5OH, 12 hr., 20	210
	p-$C_6H_4(CH$—$CHCH$—$CHC_6H_4CH_3$-$p)_2$	Quant.	C_2H_5OH, 12 hr., 20	210
	p-$C_6H_4(CH$—$CHCH$—$CHC_6H_4OCH_3$-$p)_2$	13	C_2H_5OH, 12 hr., 20	210
	p-$C_6H_4(CH$—$CHCH$—$CHC_6H_4N(CH_3)_2$-$p)_2$	Quant.	C_2H_5OH, 12 hr., 20	210
	p-$C_6H_4\left(CH$—CH—CH—CH—\underset{N}{\bigcirc}\right)_2$	35	C_2H_5OH, 2 hr., 20	108

$p\text{-}C_6H_4\big(\text{CH=CHC}_6H_5\big)_2$	C_2H_5OH, 2 hr, 40		196
$p\text{-}C_6H_4\big(\text{CH=CH—CO}_2C_2H_5\big)_2$	C_2H_5OH, 2 hr, 40	75–78	195
$p\text{-}C_6H_4\big(\text{CH=CHC}_6H_4CH_2CH_2\text{-}p\big)_2$	C_2H_5OH		196
$\left[p\text{-}C_6H_4 \begin{smallmatrix}\text{CHO}\\ \text{CH=CH}\end{smallmatrix}\right]_2$	Quant. C_2H_5OH		208

C_{40} $(C_4H_9)_3P$

$(C_6H_9)_3O$, 8 hr, reflux — 51 — 80, 271

$(C_6H_9)_3O$, 8 hr, reflux — 38 — 80, 271

$(C_6H_9)_3O$, 8 hr, reflux — 55 — 80, 271

$(C_4H_9)_3P$ ...C≡C... $(C_6H_9)_3O$, 8 hr, reflux — 42 — 80, 271

Note. References 391 to 601 are on p. 490.

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TABLE VI—Continued

OLEFINS PREPARED BY THE WITTIG REACTION

B. Bis-ylides as Starting Materials—Continued

Title	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C₁₉ (contd.) (C₆H₅)₃P=CH— ... with CH₃, CH₃	C₆H₅CH=CH—CHC₆H₅ ... with CH₃, CH₃	30	C₂H₅OH, 2 hr., 20	103
(C₆H₅)₃P=CH— ...	C₆H₅CH=CHCH=CH—CH=CHC₆H₅ ... with CH₃	75	C₂H₅OH, 12 hr., 20	210
C₂₈ (C₆H₅)₃P=CH— (biphenyl)	CH₂=CH— (biphenyl)	80	C₂H₅OH, 20	187
C₃₀ (C₆H₅)₃P=CH— (biphenyl)	CH₃— ...CH=CH₂	65–70	C₂H₅OH, 20	187
[—CH=CH—]ₙ (pyridine)		50	C₂H₅OH, 2 hr., 20	109

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	C_2H_5OH, 2 hr., 20	198
	C_2H_5OH, 2 hr., 20	199
27		
	C_2H_5OH	200
45–46		
	C_2H_5OH, 14 hr., reflux	201a
34		

C_{20}

$CH=P(C_6H_5)_3$

$CH=P(C_6H_5)_3$

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AUTHOR INDEX, VOLUMES 1–14

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Numbers in boldface type refer to experimental procedures